In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS
No. 16-393V
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A.T., Petitioner, v. SECRETARY OF HEALTH AND HUMAN SERVICES, Respondent.	Special Master Horner Ruling on the Written Record; Narcolepsy Cataplexy Syndrome; Human Papillomavirus ("HPV") vaccine

Danielle Strait, Maglio Christopher & Toale, P.A., Seattle, WA, for petitioner.
Catherine Stolar, U.S. Department of Justice, Washington, DC, for respondent.

DECISION[1]

On March 29, 2016, petitioner, A.T.[2], filed a petition under the National Childhood Vaccine Injury Act, 42 U.S.C. § 300aa-10-34 (2012),[3] alleging that her receipt of a second human papillomavirus ("HPV") vaccine on May 1, 2013 caused-in-fact, or alternatively, significantly aggravated her narcolepsy with cataplexy.[4] (ECF No. 1.) For the reasons set forth below, I conclude that petitioner is not entitled to an award of compensation.

[1] When this decision was originally filed the undersigned advised his intent to post it on the United States Court of Federal Claims' website, in accordance with the E-Government Act of 2002. 44 U.S.C. § 3501 note (2012) (Federal Management and Promotion of Electronic Government Services). In accordance with Vaccine Rule 18(b), petitioner filed a timely motion to redact certain information. This decision is being reissued with petitioner's name reduced to initials. Except for those changes and this footnote, no other substantive changes have been made. This decision will be posted on the court's website with no further opportunity to move for redaction.

[2] Petitioner was a minor when the petition was filed, so her mother filed the petition as her legal representative. Petitioner reached the age of majority on March 27, 2017 and was substituted as petitioner on December 19, 2017. (ECF Nos. 30, 31.)

[3] All references to "§ 300aa" below refer to the relevant section of the Vaccine Act at 42 U.S.C. § 300aa-10-34.

[4] The brand name of the HPV vaccine administered to petitioner is Gardasil. (*See* Ex. 21.)

I. Applicable Statutory Scheme

Under the National Vaccine Injury Compensation Program, compensation awards are made to individuals who have suffered injuries after receiving vaccines. In general, to gain an award, a petitioner must make a number of factual demonstrations, including showing that an individual received a vaccination covered by the statute; received it in the United States; suffered a serious, long-standing injury; and has received no previous award or settlement on account of the injury. Finally – and the key question in most cases under the Program – the petitioner must also establish a causal link between the vaccination and the injury. In some cases, the petitioner may simply demonstrate the occurrence of what has been called a "Table Injury." That is, petitioners may show that they suffered an injury of the type enumerated in the "Vaccine Injury Table," corresponding to the vaccination in question, within an applicable time period following the vaccination also specified in the Table. In such cases, the Table Injury is presumed to have been caused by the vaccine. § 300aa-13(a)(1)(A); § 300 aa-11(c)(1)(C)(i); § 300aa-14(a); § 300aa-13(a)(1)(B).

In many cases, however, the vaccine recipient may have suffered an injury not covered by the Vaccine Injury Table. In these "off-Table" cases, an alternative means exists to demonstrate entitlement to a Program award. The petitioner may demonstrate entitlement by showing that the recipient's injury was "caused-in-fact" by the vaccine they received, a showing often referred to as "actual causation." § 300aa-13(a)(1)(B); § 300aa-11(c)(1)(C)(ii). In off-table cases, the presumptions available under the Vaccine Injury Table are inoperative, and the burden is on the petitioner to introduce evidence demonstrating that the vaccination was responsible for the injury in question. *Althen v. Sec'y of Health & Human Servs.*, 418 F.3d 1274, 1278 (Fed. Cir. 2005); *Hines v. Sec'y of Health & Human Servs.*, 940 F.2d 1518, 1525 (Fed. Cir. 1991).

To show actual causation, petitioner must satisfy the "preponderance of the evidence" standard, the same standard ordinarily used in tort litigation. § 300aa-13(a)(1)(A); *see also Althen*, 418 F.3d at 1279; *Hines*, 940 F.2d at 1525. Under that standard, the petitioner must show that it is "more probable than not" that the vaccination caused the alleged injury. *Althen*, 418 F.3d at 1279. The petitioner need not show that the vaccination was the sole cause of the injury or condition, but must demonstrate that the vaccination was a "substantial factor" and a "but for" cause. *Shyface v. Sec'y of Health & Human Servs.*, 165 F.3d 1344, 1352 (Fed. Cir. 1999). This standard has been interpreted to require "proof of a logical sequence of cause and effect showing that the vaccination was the reason for the injury;" the logical sequence must be supported by "reputable medical or scientific explanation, *i.e.*, evidence in the form of scientific studies or expert medical testimony." *Althen*, 418 F.3d at 1278; *Grant v. Sec'y of Health & Human Servs.*, 956 F.2d 1144, 1148 (Fed. Cir. 1992). A petitioner may not receive a Vaccine Program award based solely on his or her assertions; rather, the petition must be supported by either medical records or by the opinion of a competent physician. § 300aa-13(a)(1).

In what has become the predominant framing of this burden of proof, the *Althen* court described the "causation-in-fact" standard, as follows:

> Concisely stated, Althen's burden is to show by preponderant evidence that the vaccination brought about her injury by providing: (1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of proximate temporal relationship between vaccination and injury. If Althen satisfies this burden, she is "entitled to recover unless the [government] shows, also by a preponderance of the evidence, that the injury was in fact caused by factors unrelated to the vaccine."

Althen, 418 F.3d at 1278 (citations omitted). The *Althen* court noted that a petitioner need not necessarily supply evidence from medical literature supporting petitioner's causation contention, so long as the petitioner supplies the medical opinion of an expert. *Id*. at 1279-80. That expert's opinion must be "sound and reliable." *Boatmon v. Sec'y of Health & Human Servs*., 941 F.3d 1351, 1359-60 (Fed. Cir. 2019). The *Althen* court also indicated, however, that a Program fact finder may rely upon "circumstantial evidence," which the court found to be consistent with the "system created by Congress, in which close calls regarding causation are resolved in favor of injured claimants." *Althen,* 418 F.3d at 1280.

Where a petitioner in an off-Table case is seeking to prove that a vaccination aggravated a pre-existing injury, petitioners must also establish three *additional* factors. *See Loving v. Sec'y of Health & Human Servs.*, 86 Fed. Cl. 135, 144 (Fed. Cl. 2009) (combining the first three *Whitecotton* factors for claims regarding aggravation of a Table injury with the three *Althen* factors for off table injury claims to create a six-part test for off-Table aggravation claims); *see also W.C. v. Sec'y of Health & Human Servs.*, 704 F.3d 1352, 1357 (Fed. Cir. 2013) (applying the six-part *Loving* test.). The additional *Loving* factors require petitioners to demonstrate aggravation by showing: (1) the vaccinee's condition prior to the administration of the vaccine, (2) the vaccinee's current condition, and (3) whether the vaccinee's current condition constitutes a "significant aggravation" of the condition prior to the vaccination. *Id*.

In this case, petitioner filed her petition alleging that her receipt of a second HPV vaccine caused, or alternatively, significantly aggravated her narcolepsy. (ECF No. 1.) However, petitioner now contends only that the HPV vaccine significantly aggravated her narcolepsy. (*See* ECF Nos. 26-28, 73.) Because this injury is not listed as a Table Injury relative to the HPV vaccine, petitioner must satisfy the six-part *Loving* test. *See* 42 C.F.R. § 100.3(a).

II. Procedural History

Petitioner's mother filed a petition on her behalf on March 29, 2016. (ECF No.1.) Petitioner was later substituted as petitioner once she reached the age of majority. (ECF Nos. 30, 31.) The case was assigned to Special Master Laura Millman. (ECF No.

4.) Petitioner filed supporting medical records marked as Exhibits 1-7 on April 7, 2016. (ECF No. 6.) Following an initial status conference on May 19, 2016, petitioner submitted additional medical records, petitioner's mother's affidavit, and a Statement of Completion. (Exs. 8-12, ECF Nos. 9, 11, 12.)

On May 19, 2016 Special Master Millman issued an order, noting that statements made by petitioner's mother in her medical records regarding symptom onset "[we]re not consistent." (ECF No. 8.) Special Master Millman observed that petitioner's mother reported on May 11, 2013 "that [petitioner's] narcolepsy worsened two weeks before [petitioner] received the Gardasil vaccine," but claimed "just three days later on May 14, 2013," that petitioner's "symptoms increased after she received the vaccination." (ECF No. 8 (citing Ex. 4, pp. 52, 63).)

On August 23, 2016 Special Master Millman issued a subsequent order, and again noted that "[petitioner's] medical records show that she was experiencing symptoms of narcolepsy cataplexy syndrome before she received her second Gardasil vaccine on May 1, 2013." (ECF No.13, citing Ex. 4, p. 52; Ex. 11, pp. 2, 31.) Special Master Millman ordered petitioner's mother to file an affidavit explaining the discrepancy in the records regarding the alleged onset of her daughter's injury. (*Id*.) Petitioner's mother filed an affidavit on September 22, 2016 wherein she alleged that "[t]here was nothing wrong with my daughter on May 1, 2013. She was given two vaccines that day, hepatitis and the second Gardasil." (ECF No. 14, Ex. 13, p. 1.)

Following a telephonic status conference, on September 26, 2016 Special Master Millman noted that she felt this was a significant aggravation case and ordered petitioner to file an expert report supporting her claim. (ECF. No. 15.) On November 27, 2017, Special Master Millman issued an order questioning whether it was reasonable to proceed. (ECF No. 26.) Concurrently, Special Master Millman filed Court Exhibit 1, an epidemiological study "showing that among almost one million adolescent girls, [the] HPV vaccine was not [r]elated causally to narcolepsy." (ECF No. 26.)[5] On December 11, 2017, Special Master Millman granted petitioner's Motion for Clarification, finding this case to be an allegation that petitioner's second HPV vaccine significantly aggravated her preexisting narcolepsy-cataplexy. (ECF Nos. 27, 28.)

On February 8, 2018, petitioner filed her first expert report from Dr. Lawrence Steinman and additional medical literature. (ECF Nos. 39-41, Exs. 14-39.) On May 18, 2018, respondent filed his Rule 4(c) report, arguing that the evidence presented did not meet petitioner's burden and recommending against compensation. (ECF No. 46.) Respondent also filed medical literature and expert reports from Dr. Maryann Deak (neurology and sleep medicine) (Ex. A) and Dr. Lindsay Whitton (virology and immunology) on the same day. (Ex. C) (ECF No. 43.) Each party subsequently filed

[5] Special Master Millman also noted the increased incidence of narcolepsy following the Pandemrix (2009 H1N1 flu vaccine) and the H1N1 flu virus "suggests that that the flu virus in the 2009 H1N1 flu vaccine, not the adjuvant, was responsible for the increase in narcolepsy cases. HPV does not contain H1N1 flu virus." (ECF No. 26, p. 2.)

additional expert reports and the case was later reassigned to me on June 5, 2019. (Exs. 40, 43, 49, 55; Exs. EE, GG, KK, RR; ECF No. 57 (Notice of Reassignment).)

On August 25, 2020 I held a status conference to discuss possible resolution of petitioner's claim, proposing a resolution based on the written record. (ECF No. 71.) The parties agreed.[6] (*Id.*) Petitioner filed her Motion for a Ruling on the Record on December 18, 2020. (ECF No. 73.) Respondent filed her response to petitioner's motion on March 22, 2021 and petitioner filed her reply to respondent's response to petitioner's motion on April 13, 2021. (ECF Nos. 75, 76.)

I have determined that the parties have had a full and fair opportunity to present their cases and that it is appropriate to resolve this issue without a hearing. *See* Vaccine Rule 8(d); Vaccine Rule 3(b)(2); *Kreizenbeck v. Sec'y of Health & Human Servs*., 945 F.3d 1362, 1366 (Fed. Cir. 2020) (noting that "special masters must determine that the record is comprehensive and fully developed before ruling on the record."). Accordingly, this matter is now ripe for resolution.

III. Medical History

Petitioner was born on March 27, 1999. (Ex. 2, p. 3.) Prior to vaccination, petitioner suffered only minor health issues, including a history of congenital cataract at age two and obstructive sleep apnea requiring a tonsillectomy at age five. (Ex. 3, p. 55.) On April 2, 2012, petitioner received her first HPV vaccination at 13 years of age. (Ex. 4, p. 74.) Then on May 1, 2013, petitioner presented to her pediatrician, Sidney Randel, M.D., for her routine well visit. (Ex. 4, p. 70.) Dr. Randel's physical examination of petitioner was normal.[7] (*Id.* at 71.) Dr. Randel noted "[f]ine and gross motor sensory intact," petitioner's deep tendon reflexes were equal, no pathological reflex; petitioner's tone was normal, no focal deficits; and petitioner's gait was normal and appropriate for her age. (*Id.*) He recorded that petitioner was overweight but a "well child."[8] (*Id.* at 72.) Dr. Randel discussed with petitioner a healthy diet and

[6] I also advised the parties that "[i]f upon preparing their written submissions either party comes to believe that this case is not ripe for resolution on the existing record, they may address those concerns in the form of a motion to amend the schedule. Otherwise, the parties should anticipate that I will resolve the question of petitioner's entitlement to compensation without further proceedings." (ECF No. 71.) No such motion was filed.

[7] The record notes in the section "Patient/Parent Questions," that "Mom says [petitioner] does not sleep." (Ex. 4, p. 70.)

[8] Later accounts of petitioner's symptoms reveal a history of sleep disruption and daytime sleepiness with prolonged napping prior to her hospitalization on May 11, 2013 for four to six weeks, discussed further below. (Ex. 3, p. 43, Ex. 4, p. 52 (Dr. Neidenberg); Ex. 3, p. 84-85 (Dr. Martinez); Ex. 3, pp. 5-6, Ex. 4, pp. 9-10, Ex. 11, pp. 31-33 (Dr. Dubrovsky); Ex. 3, pp. 64-67 (Dr. Brown); Ex. 3, pp. 48-50 (Dr. Maragh), Ex. 3, pp.54-55 (Dr. Chiang); Ex. 3, pp. 67-68 (Dr. Gutierrez).) In one note, petitioner described "waking up 1-2 [times] a night 4 weeks ago." (Ex. 3, p. 5.) This would place onset of petitioner's symptoms in approximately April 2013. Between 2-4 weeks prior to hospitalization, petitioner reported additional symptoms including: legs buckling (Ex. 3, p. 65, Ex. 3, p. 85), falls (Ex. 3, p. 65, Ex. 3, p. 69), slurred speech (Ex. 3, pp. 5-6), and gait difficulties (Ex. 3, p. 69, Ex. 3, p. 85). Petitioner does not allege that her narcolepsy began after the May 1, 2013 vaccination. (ECF No. 73, p. 14.)

exercise. (*Id.*) Petitioner also received a Hepatitis A vaccination and her second HPV vaccination. (*Id.* at 71.)

On May 11, 2013, ten days after receiving her second HPV vaccination, petitioner presented to the emergency department at Joe DiMaggio Children's Hospital complaining of sleeplessness, weakness, twitching and slurred speech. (Ex. 3, p. 43.) Petitioner's mother reported a history of petitioner's symptoms to Ilhana Gilderman Neidenberg, D.O. (*Id.*) The history of present illness included: a six-week history of "sleeplessness," a two-and-a-half-week history of "knees twitching while standing," and a three-day history of "slurred speech and hands twitching and shaking." (*Id.*) Petitioner's mother also remarked that "sometimes [petitioner] can[not] stand up without leaning against the wall because she is disoriented." (*Id.*) According to petitioner's mother, she had "fallen down several times" because petitioner was unaware of her fall or unable to catch herself. (*Id.*) Petitioner's history of present illness also noted that she was able to fall asleep at night, only to "wake up a few hours later unable to fall asleep." (*Id.*)

Petitioner's mother further reported to Dr. Neidenberg that she attributed petitioner's sleeplessness to the end of the soccer season, approximately six weeks prior, concluding that she "was not getting enough exercise to tire her out." (Ex. 3, p. 43.) The history of present illness also documented a six-week history of prolonged naps after school lasting three hours. (*Id.*) Petitioner's mother reported that her symptoms "have worsened so she brought [petitioner] to [primary care provider] 2 weeks ago where she received Gardasil vaccine and [the pediatrician] also recommended melatonin for sleeplessness with no relief." (*Id.*) Petitioner was admitted to the hospital May 11, 2013 for further evaluation. (*Id.* at 46.)

Later that day, petitioner was seen by Diana Martinez, M.D., for a neurology consult. (Ex. 3, p. 47) CT and EEG results were reviewed as normal. (*Id.* at 56.) The MRI was reported as normal and the MRA of the brain was inconclusive due to interference from petitioner's braces. (*Id.* at 58.) Dr. Martinez recommended a thyroid function test and that infectious disease be contacted to see whether "this could possibly be a side effect of [G]ardasil, although [she had] never seen this." (*Id.* at 90.) In her neurological exam Dr. Martinez observed that "when [petitioner] got up to use the bathroom she felt loss of balance and had some twitches…." (*Id.* at 92.)

On May 12, 2013 Dr. Martinez returned for a follow-up and noted in the subjective portion of the medical record that petitioner's "[m]other has concerns that the [petitioner] had a [G]ardasil immunization a[nd] this may have contributed to the [petitioner's] symptoms." (*Id.* at 99-100.) Dr. Martinez's assessment noted that "the etiology of [petitioner's] symptoms [is] unknown[;] it's possible that this is related to the green coffee extract [petitioner] was taking." (*Id.* at 102.)

On May 13, 2013, pediatric neurologist Tatyana Dubrovsky, M.D., met with petitioner and noted that petitioner had received a "Gardasil vaccination 2 weeks ago." (Ex. 3, p. 5.) Dr. Dubrovsky questioned whether "the vaccination has anything to do

with the escalat[ion] of the symptoms" petitioner was experiencing. (*Id.* at 6.) In the physical exam, Dr. Drubrovsky noted that petitioner "actually had an episode" where she began slurring her speech and nodding her head. (*Id.*) The same day, pediatric infectious disease specialist Robert Reid, M.D., examined petitioner for "suspected toxicity from Gardasil vaccine." (*Id.* at 51.) Dr. Reid concluded that petitioner's condition was "not likely a reaction to the vaccine since the symptoms of insomnia started way before the vaccine was given." (*Id.* at 53.)

On May 14, 2013, petitioner was seen by pediatric neurologist Stuart Brown, M.D. (Ex. 3, pp. 65-66.) Dr. Brown noted that petitioner received a Gardasil vaccination approximately two weeks prior and "[s]ince that time, her symptoms have seemingly increased, but she has also been noticing, and the mother has been noticing, that in the last week she has not only been falling, but she has been having difficulty in walking, being very unsteady on her feet." (*Id.* at 65.) Dr. Brown also questioned whether petitioner's Gardasil vaccination "triggered [] narcolepsy on an autoimmune basis," and observing that "[t]his has been reported occasionally with other immunizations." (*Id.* at 66.) Dr. Brown further commented that "[a]lthough Gardasil was thought to perhaps be associated with increased precipitation of Guillain-Barre Syndrome, the statistics for this are questionable as to a cause and effect relationship." (*Id.*)

On May 15, 2013, petitioner was seen by pediatric infectious disease specialist Maria Gutierrez, M.D. (Ex. 3, p. 68.) In her consultation, Dr. Gutierrez noted that "[s]ome sleep disturbance, narcolepsy, have been associated with previous infections. There have also been cases of narcolepsy associated with Influenzae [sic] vaccine with an adjuvant that is not available in this country." (*Id.* at 70.) Dr. Gutierrez also observed that petitioner "had received the Gardasil [vaccination] after the symptoms had started" and "d[id] not believe there has been association." (*Id.*) On May 16, 2013 petitioner had a consultation with pediatric allergist and immunologist Gary Kleiner, M.D. (Ex. 3, p. 62.) Dr. Kleiner noted that petitioner's "mother believes that some of [petitioner's] symptoms may have occurred shortly after her Gardasil vaccination." (*Id.* at 62-63.) Dr. Kleiner requested a follow-up visit to review petitioner's pending lab results. (*Id.* at 63-64.) Petitioner's lab results ultimately revealed that she had the HLA DQB1*0602 gene and low hypocretin, consistent with narcolepsy.[9] (Ex. 2, p. 4; Ex. 11, p.103.)

Petitioner was discharged from the hospital on May 17, 2013 after receiving intravenous immunoglobulin for treatment of possible autoimmune narcolepsy. (Ex. 3, p. 72; Ex. 11, p. 2.) The discharge summary, dated May 16, 2013, indicates that petitioner was seen by two infectious disease physicians, Drs. Reid and Gutierrez, and three neurologists, Drs. Martinez, Dubrovsky and Brown and that her "presumptive diagnosis [wa]s narcolepsy." (Ex. 11, p. 3.) Her symptoms were listed as "ongoing but not worsening." (*Id.*) On May 23, 2013 petitioner returned to see Dr. Dubrovsky for a follow-up appointment. (Ex. 11, p. 31.) The history of present illness noted that

[9] It is not clear from the records when these lab results were reported, but petitioner appears to have been discharged prior to the tests' completion. (Ex. 11, pp. 3-7) (lab results available at discharge do not include hypocretin or genetic testing results) (*But see* Ex. 2, p. 4; Ex. 11, p. 103) (reporting test results from May 14, 2013).)

petitioner "presented with excessive daytime sleepiness, cataplexy, and episodes of sleep paralysis since mid-April, exacerbated after Gardasil shot at the end of April." (*Id.*) Per her assessment, Dr. Dubrovsky noted that she was "not certain[] if the symptoms are associated with the vaccination, but would recommend to report it to the registry." (*Id.*)

On June 27, 2013 petitioner consulted with pediatric neurologist Marcel Deray, M.D. (Ex. 7, p. 126.) The history of petitioner's present illness noted that her narcolepsy symptoms "[s]tarted with insomnia in April 2013." (*Id.*) Dr. Deray noted that petitioner saw her primary care provider on May 1, 2013 for a routine visit and was started on 3 mg of melatonin. (*Id.*) Dr. Deray also noted that petitioner received a "Gardasil [*sic*] shot and another Hep A vaccine" during that visit. (*Id.*) Dr. Deray remarked that petitioner's left leg buckled three days after her vaccinations, the "[f]ollowing day speech was slurred," and "[f]ive days after the shot, at dinner, [her] right arm would shake." (*Id.*) Dr. Deray's impression was narcolepsy with cataplexy syndrome and petitioner was prescribed Ambien. (*Id.* at 129.) Petitioner's mean sleep latency test ("MSLT") conducted in June of 2013 recorded REM onset sleep periods at 5/5 and an msl of 1.6 min., although a follow-up study in August of 2013 was normal. (Ex. 7, pp.110, 138.)

On October 17, 2013 petitioner returned to see Dr. Dubrovsky, who confirmed petitioner's diagnosis of narcolepsy cataplexy syndrome. (Ex. 11, p. 104.) In this visit, Dr. Dubrovsky noted that petitioner's "mother [] want[ed] to clarify the history, the [petitioner] started having difficulty staying asleep and taking daytime naps since mid-April. She had Gardasil shot on 5/1/13 and since then developed sleep attacks and cataplexy that was debilitating." (*Id.* at 103.) Dr. Dubrovsky suggested scheduled naps and continued petitioner's prescriptions for Ambien and Concerta. (*Id.* at 103-104.)

Petitioner was later prescribed Xyrem for her narcolepsy, and continued treatment with Dr. Deray throughout the rest of 2013 and until March 2016. (*See* Ex. 9, pp. 2-10.) As of December 2019, petitioner was seeing pulmonologist Samuel Gurevich, M.D., regarding treatment for excessive daytime somnolence, narcolepsy, and parasomnias. (Ex. 53, p. 24.) Petitioner's most recent records, from July 23, 2020, indicate that she is participating in weekly psychotherapy for reasons unrelated to the condition at issue in this case. (Ex. 54, p. 1.)

a. Petitioner's Mother's Affidavits

In her first affidavit, petitioner's mother avers that petitioner received the Gardasil vaccine and "sustained Narcolepsy cataplexy syndrome, which was actually caused by the vaccine received." (Ex. 10, p. 1.) In response to Special Master Millman's order, petitioner's mother provided a supplemental affidavit, explaining the inconsistences in petitioner's medical records. (Ex. 13.)

In her second affidavit, petitioner's mother states that "[t]here was nothing wrong with [petitioner] on May 1, 2013" during her well-child visit and petitioner had "no

medical problems that day." (Ex. 13, p. 1.) Petitioner's mother also claims that she "did note that [petitioner] was not sleeping," and "[p]rior to that visit, [petitioner] had had a work up for sleep apnea[.]" (*Id.*) According to petitioner's mother, petitioner had recently stopped playing soccer and "[she] felt at the time that the sleep issues were related to a lack of exercise which would result in being less tired at bed time." (*Id.*) She added that this visit was "entirely a routine check-up and [] [petitioner] was cleared for participation in athletics at its conclusion." (*Id.*)

Petitioner's mother avers that the history of present illness recorded in petitioner's hospital discharge record from May 16, 2013 appears to be "an accurate narrative of what I remember to be the time line of events before and after May 1, 2013." (Ex. 13, p. 1-2 (citing Ex. 11, p. 2).) Prior to May 1, 2013, petitioner's mother claims that "the only noteworthy issue involving [petitioner's] health was her problems falling asleep." (*Id.* at 2.) However, she states that "that issue was NOT what brought us to the pediatrician that day. In fact, as [she] reported on May 11, the character of [] [petitioner's] sleep issues changed dramatically in the week before May 11." (*Id.*)

Petitioner's mother also avers that she has "no independent memory of saying that [petitioner's] narcolepsy/cataplexy symptoms began in April," and that "at the time of the May 11 admission [of petitioner to the hospital]," petitioner's mother "felt that her symptoms began after the May 1 Gardasil vaccine." (Ex. 13, p. 2 (citing Ex. 11, p. 31).) She is unsure "where the individual who wrote that history got the April dates referenced," and she does not believe that "[she] would have made the mistake of saying that the symptoms had begun in April." (*Id.*) Regardless, her mother states that petitioner's symptoms did not start until after May 1. (*Id.*)

Petitioner's mother further avers that the history given to Dr. Gilderman Neidenberg on May 11, 2013 which "suggests that [petitioner's] narcolepsy/cataplexy symptoms started in early April 2013" was in fact "wrong." (Ex. 13, p. 2 (citing Ex. 4, p. 52.).) Additionally, petitioner's mother asserts that the history written by Dr. Randel during her daughter's well-child visit on May 1, 2013, and the history given by Dr. Lazar at discharge "reflect what [she] remember[s] about the onset of [petitioner's] narcolepsy/cataplexy." (Ex. 13, p. 2 (citing Ex. 11, pp. 2, 52-56).) Though the record suggests that she took petitioner to her primary care physician on May 1 "because of worsened narcolepsy symptoms," petitioner's mother states that she did not. (Ex. 13, p. 3.) She maintains that petitioner's May 1 visit "was a well-child visit only." (*Id.*)

IV. Expert Opinions

a. Petitioner's expert, Lawrence Steinman, M.D., initial report

Dr. Steinman received his medical degree from Harvard in 1973. He is currently a professor of the department of neurology at Stanford University. (Ex. 14, p. 1.) Dr. Steinman has treated patients, both adults and children, who suffered from various forms of autoimmune disease of the nervous system, including optic neuritis, ADEM, Bechet's disease, inflammatory neuropathy, transverse myelitis, neuromyelitis optica

(NMO), and multiple sclerosis (MS). (*Id*.) Dr. Steinman's research focuses on how the immune system attacks the nervous system and he has published on the subject of narcolepsy. (*Id.* at 1-3.) He holds over 50 American and European patents, including several U.S. patents relating to vaccines. (*Id*. at 5.)

Dr. Steinman opines that petitioner's HPV vaccination on May 1, 2013 "caused a significant aggravation of a sleep disorder, leading to narcolepsy that was explicitly diagnosed two weeks thereafter." (Ex. 14, p. 1.) Dr. Steinman's theory on how the HPV vaccination "trigger[ed] narcolepsy" relies on the principles of molecular mimicry. (*Id.* at 9.) According to his theory, the Gardasil vaccine[10] contains molecular mimics of hypocretin, also called orexin[11], and hypocretin-2 receptor, also known as the orexin-2 receptor. (*Id.*) Dr. Steinman notes three groups who have "reported immune responses to hypocretin reception 2 in narcolepsy": (i) a group led by Dr. Steinman who found that "in vaccine-induced narcolepsy, there are antibodies to HCRT-R2" and who identified a region of the HCRT-R2 molecule located at the site where hypocretin binds the receptor[12] (ii) a group in Japan which found antibodies to HCRT-R2 in narcolepsy[13] and (iii) as did a group from Oxford.[14] (*Id.* at 10.) Dr. Steinman also mentions a fourth group, Mignot's group, who showed "some evidence of antibodies to HCRT-R2 in narcolepsy," though he discounts these findings due to a "major flaw" in one of the assays for HCRT-R2 that appears in their supplementary data. (*Id.* (citing (citing De la Herrán-Arita et al., *CD4⁺ T cell Autoimmunity to Hypocretin/Orexin and Cross-Reactivity to a 2009 H1N1 Influenza A Epitope in Narcolepsy,* 5(216) SCI. TRANSL. MED. 1-13 (2013) (Ex. 25); De la Herrán-Arita et al., *CD4⁺ T cell Autoimmunity to Hypocretin/Orexin and Cross-Reactivity to a 2009 H1N1 Influenza A Epitope in Narcolepsy,* 5(216) SCI. TRANSL. MED. 1-13 (2013) (Retraction published on July 30, 2014) (Ex. 26)).)

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[10] Petitioner received the Gardasil Quadrivalent HPV vaccine on May 1, 2013, which contains the L1 proteins from four different strains of HPV: HPVs 6, 11, 16, and 18. (Ex. 14, p. 9 (citing Ex. 21)). Presently, "Gardasil-9 (Merck), a nine-valent HPV vaccine (9vHPV) that protects against HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58, is the only HPV vaccine currently distributed in the U.S." *What Ty[es of HPV Vaccines Are There?,* CDC, https://www.cdc.gov/vaccines/vpd/hpv/public/index.html (last updated Mar. 17, 2020).

[11] "Either of two neuropeptides (orexin A and orexin B) produced in the hypothalamus and regulating feeding behavior as well as the sleep-wake cycle." *Orexin,* DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=13359 (last visited Sept. 8, 2021).

[12] Ahmed et al., *Antibodies to influenza nucleoprotein cross-react with human hypocretin receptor 2,*7 (294) SCI. TRANSL. MED. (2015) (Ex. 27). Dr. Steinman notes that his group identified the region of the HCRT-R2 molecule that was previously identified at the University of Texas Southwestern Medical School, "precisely at the site where hypocretin binds the receptor." (Ex. 14, p. 10) (citing Yin et al, *Structure and ligand-binding mechanism of the human OX1 and OX2 orexin receptions,* 23(4) NAT. STRUCT. MOL. BIOL. 293-9 (2016)).)

[13] Tanaka et al., *Detection of autoantibodies against hypocretin, hcrtr1, and hcrtr2 in narcolepsy: anti-hcrt system antibody in narcolepsy,* 29(5) SLEEP 633-638 (2006) (Ex. 29).

[14] Giannocarro et al., *Antibodies against HCRT-R2 are rare in narcolepsy,* 40(2) SLEEP (2017) (Ex. 30.)

Dr. Steinman carried out BLAST[15] searches to identify homologies between the components of the Gardasil vaccine and various components of the hypocretin pathway, including hypocretin itself and the HCRT-R2 receptor. (Ex. 14, p. 11.) Dr. Steinman classifies his criteria for a "meaningful molecular mimic" as a run of 5 or more of 12 amino acids that are identical. (*Id.*) Based on his own published research, Dr. Steinman opines that the identity of 5 of 12 amino acids, or sometimes even 4 or 11 amino acids, were sufficient to "trigger experimental neuroinflammation with paralysis." (*Id.* (citing Gautam et al, *A polyalanine peptide containing only five native myeline basic protein residues induces autoimmune encephalomyelitis,* 127 JOURNAL OF EXPERIMENTAL MEDICINE 605-609 (1992) (Ex. 32); Gautam et al., *Minimum structural requirements for peptide presentation by major histocompability complex class II molecules: Implications in induction of autoimmunity,* 91 PROC. NATL. ACAD. SCI. USA 767-771 (1994) (Ex. 33); Gautam et al., *A viral peptide with limited homology to a self-peptide can induce clinical sign of experimental autoimmune encephalomyelitis,* 161 J. IMMUNOL., 60-64 (1998) (Ex. 34)).) He also adds that the 5/12 or 4/11 amino acids that are identical need not be consecutive. (*Id.*)

Through his BLAST searches, Dr. Steinman identified several homologies between the human protein (hypocretin and hypocretin-2 receptor) and the HPV proteins that were 5/12 or better. (Ex. 14, pp. 14-25.) Dr. Steinman acknowledges that his report only includes the "positive" or "relevant" searches, though "[m]any searches were performed where the criterion" were not met. (*Id.* at 25.) In support of his theory, Dr. Steinman cites a paper by Ufret-Vicenty et al., whose experiments passively transferred T cells that cross-reacted with myelin basic protein and HPV (in mice) and found that the experimental animals became paralyzed. (*Id.* at 25-26 (citing Ufret-Vincenty et al., *In Vivo Survival of Viral Antigen—specific T Cells that Induce Experimental Autoimmune Encephalomyelitis,* 188 JOURNAL OF EXPERIMENTAL MEDICINE 1725-1738 (1998) (Ex. 35)).) However, it is not possible to test petitioner for immunity to these mimics. (*Id.* at 26.)

Dr. Steinman acknowledges that "[m]olecular mimicry may indeed be widespread." (Ex. 14, p. 26.) He explains "[o]ther genetic and environmental factors" are necessary before these self-reactive immune responses to HCRT-R2 may trigger an immune response. (*Id.* at 28-29.) He maintains that his theory of molecular mimicry, nonetheless, is a "key mechanism" in understanding how the vaccination may cause injury. (*Id.*)

In response to Court Exhibit 1, Dr. Steinman suggests that this epidemiological study, in fact, shows an increased rate of narcolepsy among those who received the Gardasil vaccine. (Ex. 14, p. 29.) According to Dr. Steinman, the 2.61 cases of

[15] According to its own website, the Basic Local Alignment Search Tool (BLAST) "finds regions of local similarity between sequences. The program compares nucleotide or protein sequences to sequence databases and calculates the statistical significance of matches. BLAST can be used to infer functional and evolutionary relationships between sequences as well as help identify members of gene families." *See* https://blast.ncbi.nlm.nih.gov/Blast.cgi (last visited Dec. 2, 2021).

narcolepsy per 10^5 in the vaccinated group versus the 1.81 cases per 10^5 in the unvaccinated group indicates that the Gardasil vaccine is associated with a higher rate of narcolepsy compared to the unvaccinated, "even though it may not reach so-called 'statistical significance.'" (*Id.* at 31.)

Finally, Dr. Steinman opines that petitioner's HPV vaccination on May 1, 2013, "changed the trajectory of the case." (Ex. 14, p. 31.) Dr. Steinman remarks that "though there were symptoms prior to the May 1, 2013 immunization, there was clear worsening about 10 days after the May 1, 2013, Gardasil shot." (*Id.*) Dr. Steinman quotes the "history of present illness" in Dr. Lazar's discharge summary from May 16, 2013:

> Over the past 3 days she reports to "twitching" of her left upper extremity and left leg lasting for approximately 20 seconds followed by a tingling sensation in her hands. She would have approximately 2 episodes per day. During these "twitching" episodes she would be fully awake and states that she would use her right hand to hold on to her left upper extremity while it was jerking but this would not stop the jerking movements. She also reports recent episodes of light headedness and fell twice 2 days ago and once today.

(*Id.*)

Dr. Steinman stresses that "[t]his type of activity was NOT present prior to the May 1, 2013, immunization, based on the contemporaneous record." (*Id.*) (emphasis in original). According to Dr. Steinman, the progression of petitioner's symptoms is consistent with the progression of narcolepsy in patients studied in Finland and England who received the Pandemrix vaccination. (*Id.* at 32 (citing Partinen et al., *Increased Incidence and Clinical Picture of Childhood Narcolepsy following the 2009 H1N1 Pandemic Vaccination Campaign in Finland,* 7 PLoS ONE e33723 (2012) (Ex. 38); Winstone et al., *Clinical features of narcolepsy in children vaccinated with AS03 adjuvanted pandemicA/H1N1 2009 influenza vaccine in England,* 56 Dev. Med. Child. Neurol. 1117-1123 (2014) (Ex. 39).)

b. Respondent's expert, Maryann Deak, M.D., initial report

Dr. Deak received her medical degree from Georgetown University School of Medicine in 2004. (Ex. B.) Dr. Deak currently serves as the Associate Medical Director in Sleep Medicine for eviCore Healthcare. (Ex. A.) Dr. Deak is board certified in both neurology and sleep medicine, with significant clinical experience treating sleep disorders, including narcolepsy and other hypersomnia. (*Id.*) She completed a clinical and research fellowship in sleep medicine at Brigham and Women's Hospital and Harvard Medical School in 2010. (*Id.*)

Dr. Deak opines that the presence of narcolepsy symptoms prior to vaccination, the evolution of petitioner's symptoms consistent with pediatric narcolepsy, and the lack

of evidence supporting an increased risk of narcolepsy with Gardasil, taken together, show no causal link between the Gardasil vaccination and petitioner's narcolepsy. (Ex. A.) Both Drs. Steinman and Deak agree that petitioner developed symptoms of narcolepsy prior to petitioner's May 1, 2013 vaccination. (Ex. 14, p. 31; Ex. A, p. 4.) Dr. Deak notes that petitioner presented with symptoms of sleep disruption and daytime sleepiness with prolonged napping 4-6 weeks prior to her hospitalization. (Ex. A, p. 4 (citing Exs. 3, 4).) While petitioner's symptoms of sleep paralysis, cataplexy, slurred speech and gait difficulties appeared 2-4 weeks prior to hospitalization. (Ex. A, p. 4.)

Dr. Deak explains that the full narcoleptic tetrad of symptoms–excessive daytime sleepiness, cataplexy, hypnagogic/hypnopompic hallucinations and sleep paralysis–is rarely present at initial presentation. (Ex. A, p. 5.) The order in which symptoms appear can also vary. (*Id.* (citing Dauvilliers et al., *Narcolepsy with Cataplexy,* 369 THE LANCET 499-511 (2007) (Ex. H)).) Due to the "insidious onset" of narcolepsy, as well as accompanying behavioral, metabolic, and mood symptoms, narcolepsy is often misdiagnosed. (Ex. A, p. 5.) Dr. Deak notes that in more than 80% of cases cataplexy develops within two to three months; disturbed night sleep is reported in more than 90% of narcolepsy type 1 patients; and more than 70% of patients report a decrease in academic performance. (Ex. A, pp. 5-6 (citing Dauvilliers et al., *supra,* at Ex. H. p. 499-511).); Aran et al., *Clinical and therapeutic Aspects of Childhood Narcolepsy-Cataplexy: a Retrospective Study of 51 Children,* 33 SLEEP 1457 (2010) (Ex. I).)

Dr. Deak likewise notes that narcolepsy is caused by hypocretin deficiency, likely due to the selective loss of hypocretin-producing neurons in the hypothalamus. (Ex. A, p. 6.) She adds that the autoimmune hypothesis is the leading theory for narcolepsy type 1, due to a strong association between narcolepsy type 1 and the human leukocyte antigen (HLA) DQB1*0602. (*Id.*) Dr. Deak also notes that (i) seasonal differences in narcolepsy incidence, (ii) the rise in incidences post 2009-2010 administration of the AS03-adjuvanted H1N1 vaccine and (iii) the association with anti-streptococcal antibodies all support the theory that environmental factors contribute to the development of narcolepsy in patients who are genetically susceptible. (*Id.* citing Postiglione et al., *the Clinical Spectrum of Childhood Narcolepsy,* 5 SLEEP MED. REV. 70-85 (2018) (Ex. K)).) However, unlike Dr. Steinman, Dr. Deak stresses that "autoantibodies specific to hypocretin peptides have not been found," and to date, direct evidence supporting the autoimmune hypothesis is lacking. (*Id.* (citing Mignot, *Narcolepsy: Genetics, Immunology, and Pathophysiology, in* Principles and Practice of Sleep Medicine (6th ed. 2017) (Ex. O)).)

Dr. Deak questions Dr. Steinman's causation theory, suggesting that Dr. Steinman relies upon data from autoimmune disorders such as multiple sclerosis and other vaccines such as H1N1 – without presenting a causal link to Gardasil or narcolepsy. (Ex. A, p. 7.) Dr. Deak acknowledges the increased incidence of narcolepsy after the administration of the AS03-adjuvanted H1N1 vaccine in several European countries. (*Id.*) Yet, Dr. Deak stresses that there is no increased risk of narcolepsy with either H1N1 vaccines that contained other adjuvants, such as Focetria, or among non-adjuvanted H1N1 vaccines given in the United States. (*Id.* (citing

Partinen, *Narcolepsy as an Autoimmune Disease: the Role of H1N1 Infection and Vaccination,* 13 THE LANCET 600-13 (2014) (Ex. E); Duffy et al., *Narcolepsy and Influenza A (H1N1) Pandemic 2009 Vaccination in the United States,* 83 NEUROL. 1823-30 (2014) (Ex. Q); Nguyen et al., *Vaccine-Associated Inflammatory Disease of the Central nervous System: Form Signals to Causation,* 29 CURR. OPIN. NEUROL. 1-10 (2016) (Ex. R).)

Lastly, Dr. Deak contends that Court Exhibit 1, the Arnheim-Dahlstrom et al. study does not demonstrate any significant association between narcolepsy and HPV vaccination. (Ex. A, p. 7.) Quoting the authors in that study, Dr. Deak notes that "this large cohort study found no evidence supporting associations between exposure to HPV vaccine and autoimmune, neurological, and venous thromboembolic adverse events." (*Id*. (citing Arnheim-Dahlstrom et al., *Autoimmune Neurological, and Venous Thromboembolic Adverse Events After Immunisation of Adolescent Girls with Quadrivalent Human Papillomavirus Vaccine in Denmark and Sweden: Cohort Study,* 347 Brit. Med. J. 1-11 (2013) (Ex. S.))

c. Respondent's expert, J. Lindsay Whitton, M.D., Ph.D., initial report

Dr. Whitton received his medical degree from the University of Glasgow in 1979 and his doctorate degree in virology (focusing on herpesvirus transcription) also from the University of Glasgow in 1984. (Ex. D.) Dr. Whitton has not sought licensure in the United States, nor has he practiced medicine in the United States.[16] (Ex. C.) As of the time of his submissions in this case, Dr. Whitton serves as a professor in the Department of Immunology and Microbiology at the Scripps Research Institute. (Ex. D.) He has published extensively on the adaptive and innate immune response and on molecular mimicry. (*Id.*)

Dr. Whitton likewise agrees with Drs. Steinman and Deak that the onset of petitioner's disease preceded the vaccination. (Ex. C, p. 3-4.) Dr. Whitton disagrees with Dr. Steinman's opinion that the HPV vaccine "changed the trajectory of the case" and would be a "significant aggravation." (*Id.* at 4 (citing Ex. 14, p. 6.)) Rather, Dr. Whitton opines that petitioner's disease severity "was clearly increasing prior to, or contemporaneous with, the vaccination." (Ex. C, p. 4.) Like Dr. Deak, Dr. Whitton finds that the onset and progression of petitioner's symptoms are consistent with the typical evolution of pediatric narcolepsy. (*Id.*)

Additionally, Dr. Whitton opines that there is no significant association reported between narcolepsy and the HPV vaccine. Dr. Whitton believes that Dr. Steinman's reliance on various studies of the Pandemrix vaccine and narcolepsy is misplaced. (Ex. C, pp. 4, 12-13.) According to Dr. Whitton, Dr Steinman attempts to "tar Gardasil using the Pandemrix brush." (*Id.* at 5.) Dr. Whitton stresses that Dr. Steinman's theory is "not

[16] In his report Dr. Whitton notes that while he is "medically qualified," he has never sought licensure in the United States, and he shall defer to Dr. Deak's expertise in the area of sleep disorders and diagnoses. (Ex. C at 2.)

scientifically appropriate; one cannot reasonably infer that what may happen with one vaccine must happen with all vaccines." (*Id.*) (emphasis in original.)

With regard to causation, Dr. Whitton opines that Dr. Steinman's molecular mimicry theory is not a valid causal theory for the development, or exacerbation of, narcolepsy. Dr. Whitton takes issue with Dr. Steinman's classification of a "meaningful molecular mimic." (Ex. C, p. 5.) First, he explains that in order to identify an amino acid sequence as a "mimic," one cannot rely on a shared homology alone. (*Id.*) Mimicry is defined by the "immune response that the sequence induces" and to be a "mimic" the amino acid sequence must "(i) [] trigger an immune response and, (ii), that response must recognize (i.e., cross-react with) the other peptide[.]" (*Id.*) (emphasis in original). Unless both criteria are met, then it is not a mimic, but merely a homology. (*Id.*)

With respect to Dr. Steinman's BLAST searches, Dr. Whitton notes that for the L1 protein of HPV11 and hypocretin, he found seven additional homologies of 5/12 or better; and for hypocretin receptor 2 and L1 protein HPV18, he found twenty-three additional homologies of 5/12 or better. (Ex. C, p. 6.) According to Dr. Whitton these additional "hits," demonstrate that Dr. Steinman's rare and "meaningful molecular mimics" are in fact commonplace and not meaningful. (*Id.*) Even statistical probability demonstrates how the presence of numerous homologies is entirely predictable among a large number of proteins.[17] (*Id.* at 7-10.)

Dr. Whitton also stresses that most homologies do not trigger biologically-meaningful cross-reactivity. (Ex. C, p. 11.) Dr. Whitton compared two of the L1 proteins from HPV6 and HPV 11 and found 487 homologies of 5/12 or better. (*Id.*) Following Dr. Steinman's logic, Dr. Whitton suggests that every one of these 487 homologies should trigger cross-reactive immunity. (*Id.*) And if each one of these 487 responses were "meaningful," Dr. Whitton explains, the immune response against the HPV6 L1 protein "should confer protection against both the parental virus (HPV6) and the other virus (HPV11)." (*Id.*) If this were the case, the HPV vaccine would require only one of the viral proteins to induce immune responses that would protect against both viruses. (*Id.*) "But, of course, this isn't the biological reality." (*Id.*) Dr. Whitton therefore concludes that even when there are 487 homologies, it would be wrong to conclude that one of them must have a meaningful biological impact. (*Id.*) Studies such as Trost et al., which compared bacterial proteins against the human proteome identified *thousands* of short homologies. (*Id.* (citing Trost et al., *Bacterial peptides are intensively present throughout the human proteome,* 1 SELF NONSELF 71-74 (2010) (Ex. U)).) Dr. Whitton stresses that molecular mimicry is "real," however, the mere existence of a homology is insufficient to trigger an immune-mediated disease. (*Id.*)

Dr. Whitton notes that large studies have failed to identify any causal relationship between the HPV vaccine and several autoimmune diseases. (Ex. C, p. 12.) Dr.

[17] Dr. Whitton explains, in part, "[i]t's like being given a lottery ticket, and being told that there is a 1/32,000 chance of its being a winning ticket. You wouldn't be too excited. But if a truck delivered another 218,239 tickets to your doorstep, you'd be ecstatic." (Ex. C, p. 8.)

Whitton cites only one published scientific study which in his estimation suggests that the HPV vaccine may have autoimmune consequences. (*Id.* at 13 (citing Andrews et al., *No Increased Risk of Guillain-Barre Syndrome After Human Papilloma Virus Vaccine: a Self-Controlled Case-Series Study in England,* 35 VACCINE 1729-1732 (2017) (Ex. AA)).) Yet, he finds that the association was weak, the paper did not use clinician-validated cases of the disease and did not find any association with GBS.[18] (*Id.*) Turning to the HPV vaccine, Dr. Whitton cites a 2018 review which states:

> *We identified 109 studies, including 15 population-based* ***studies in over 2.5 million vaccinated individuals across six counties****. All vaccines demonstrated an acceptable safety profile; injection-site reactions were slightly more common for 9vHPV vaccine than for 4vHPV vaccine.* ***There was no consistent evidence of an increased risk of AESI[19], including demyelinating syndromes or neurological conditions such as complex regional pain or postural orthostatic tachycardia syndromes.*** *The risk-benefit for HPV vaccines remains highly favourable.*

(*Id.* (citing Phillips et al., *Safety of Human Papillomavirus Vaccines: an Updated Review,* 41 DRUG SAF. 329 (2018) (Ex. CC)) (emphasis in original).

Dr. Whitton likewise notes that the authors of the Arnheim-Dahlstrom et al. study–which evaluated the frequency of several diseases (including narcolepsy) appearing within a 180-day window following HPV vaccination–concluded "no significant association was observed with narcolepsy." (Ex. C, p. 14) (quoting Arnheim-Dahlstrom et al., *supra,* at Ex. S, p. 5 (2013)).) Dr. Whitton notes that Dr. Steinman's analysis of this study "ignore[s]" the statistical significance of the results, in favor of the absolute number of cases of narcolepsy in those vaccinated versus unvaccinated. (Ex. C, p. 14.)

d. Dr. Steinman's first supplemental report, Exhibit 40

In his first supplemental report, Dr. Steinman highlights the development of "twitching episodes" a few days prior to petitioner's May 11 admission as a new symptom that developed after petitioner's HPV vaccination. (Ex. 40, pp. 2-3.) Additionally, Dr. Steinman reiterates that the worsening of petitioner's symptoms over a 12-month period is consistent with studies involving narcolepsy and the H1N1 vaccine in England and Sweden. (*Id.* at 3 (citing Partinen et al., *supra,* at Ex. 38; Winstone et al., *supra,* at Ex. 39).) Dr. Steinman proposes that the Arnheim-Dahlstrom et al. study, Court Exhibit 1, "does reinforce the Petitioner's theory to the level of a 'preponderance of evidence.'" (Ex. 40, p. 7.) In the context of what Dr. Steinman describes as a "meaningful metric when the burden of proof is described as 50% and a feather," he

[18] Dr Whitton writes "[o]bviously, GBS is not claimed in the present matter. However, to my knowledge, this is the only published scientific study to suggest that HPV vaccine may have any autoimmune consequences whatsoever and, as such, it is worthy of a little dissection." (Ex. C, p. 13.)

[19] "AESI = adverse event of special interest" (Ex. C, p. 13)

suggests that the 2.4-fold increase in the upper limit for Gardasil vaccinated versus unvaccinated is significant. (*Id.* at 6-7.)

In response to criticism of his molecular mimicry theory, Dr. Steinman quotes a passage from one of Dr. Whitton's papers, in part, "showing that almost 4% of antiviral monoclonal antibodies also reacted with self proteins." (Ex. 40, p. 9 (citing Fujinami et al., *Molecular Mimicry, Bystander Activation, or Viral Persistence: Infections and Autoimmune Disease,* 19(1) CLIN. MICROBIOL. REV. 80-94, 81 (2006) (Ex. 41).) Dr. Steinman explains that "[i]f 4% of viral antibodies reacted with self-proteins, it is expected that over the life of a human subjected to viral infections, that there would be a large component of anti-viral antibodies that are also 'anti-self.'" (Ex. 40, p. 9.) Following this logic, Dr. Steinman stresses that autoimmunity is in fact widespread. (*Id.*)

Dr. Steinman explains that his references to the Pandemrix vaccine provided background, and his theory in regard to petitioner's case is based on "how the contents of the Gardasil vaccine share structural similarities with molecules that are key in narcolepsy, orexin (hypocretin) and its receptor." (Ex. 40, p. 9.) Furthermore, Dr. Steinman disputes Dr. Whitton's "simple math," and instead proposes that "these homologies are NOT inevitable." (Ex. 40, p. 10.) As evidence Dr. Steinman provides examples of his positive searches (where he identifies a homology) and negative searches (where he failed to identify a homology of an acceptable degree.) (*Id.* at 10-12.) With these searches Dr. Steinman appears to suggest that when a homology is identified (a positive search) it is therefore biologically-significant.

In response to Dr. Whitton's results (identifying 487 homologies of 5/12 or better between HPV6 and HPV11) Dr. Steinman explains that these two strains "are closely related." (Ex. 40, p. 12.) Finding a match between these two strains is "akin to marveling at how similar are members of a biologic family," according to Dr. Steinman. (*Id.*) He explains that what is significant is that HPV6 and HPV11 have "mimics of significance" with orexin, while there are no matches for HPV16 and HPV18 (though all four L1 proteins, HPV6, HPV11, HPV16 and HPV18, are present in the Gardasil vaccine). (*Id.*)

Dr. Steinman also suggests the presence of alum makes the HPV components more immunogenic. (Ex. 40, p. 13.) As a result, "[t]he Gardasil vaccine leads to a 40-fold increase in HPV antibodies compared with the physiological antibody level triggered by a natural HPV infection." (*Id.* (quoting Souayah et al., *Guillain-Barre Syndrome after Gardasil vaccination: Data from Vaccine Adverse Event Reporting System 2006-2009,* 29 Vaccine 886-889 (2011) (Ex. 42).) Dr. Steinman appears to suggest that the alum adjuvant increases the probability that a cross-reactive immune response may be induced.

e. Dr. Deak's first supplemental report, Exhibit GG

In her supplemental report, Dr. Deak opines that "[a] vaccine given in the midst of typical symptom evolution does not constitute a causal relationship." (Ex. GG, p. 1.)

While Dr. Steinman highlights the presence of hand twitching a few days prior to petitioner's admission as a new symptom that she developed post-vaccination, Dr. Deak explains that cataplexy may present differently in children than in adults. (*Id.*) Cataplexy in children may not be linked to emotional stimuli and may present as loss of muscle tone or increased motor movements. (*Id.* (citing Nevsimalova, *The Diagnosis and Treatment of Pediatric Narcolepsy,* 14 CURR. NEUROL. NEUROSCI. Rep. 469 (2014) (Ex. G); Postiglione et al, *supra,* at Ex. K).) Furthermore, Dr. Deak reiterates that petitioner was already experiencing symptoms suggestive of cataplexy prior to her vaccination. (*Id.*) That certain symptoms manifested as petitioner's narcolepsy progressed "is only evidence of the expected progression and does not constitute significant aggravation of her underlying disease course." (*Id.* at 1-2.)

Dr. Deak also takes issue with Dr. Steinman's theory of a greater-than-12-month narcolepsy onset. (Ex. GG, p. 2.) In the first article Dr. Steinman cites from Finland, Dr. Deak points out that the status and date of Pandemrix vaccination was obtained from vaccination certificates filed by health care professionals in Finland and the presence of narcolepsy symptoms and time of onset were retrospectively obtained from the medical records. (*Id.* (citing Partinen et al., *Increased incidence and clinical picture of childhood narcolepsy following the 2009 H1N1 pandemic vaccination campaign in Finland,* 7 PLOS ONE e33723 (2012) (Ex. HH)).) That study reported a mean interval of 53 days from the date of vaccination to the onset of symptoms – for children aged 17 or younger. (*Id.*) Furthermore, Dr. Deak notes that the study from England that Dr. Steinman cites is also a retrospective review, where vaccination status and time of onset was determined by questionnaires sent to general practitioners. (*Id.* (citing Winstone et al., *supra,* at Ex. 39).) In that study, Dr. Deak highlights that only eleven children received the Pandemrix vaccine prior to the onset of symptoms of narcolepsy, while seven of the eleven children received the vaccine six months or less prior to the reported onset of symptoms, and six children received the vaccine within three months. (Ex. GG, p. 2.) Generally, Dr. Deak notes that the reported timing of symptom onset is prone to recall bias. (*Id.*) Based on her own clinical experience, and the insidious nature of narcolepsy onset, Dr. Deak stresses that the onset of symptoms in a retrospective study is likely to have occurred prior to the reported time of presentation. (*Id.*)

Dr. Deak cites a retrospective study conducted in Sweden where symptom onset was determined based on medical record review and telephone interviews with parents and patients. (Ex. GG, p. 2 (citing Attila Szakacs et al., *Increased childhood incidence of narcolepsy in western Sweden after H1N1 influenza vaccination,* 80 NEUROLOGY, 1315-1321 (2013) (Ex. II)).) In that study, the median time from H1N1 vaccination to symptom onset was nine and a half weeks, with nineteen of the twenty-eight patients developing symptoms in twelve weeks or less. (*Id.*) Additionally, Dr. Deak cites a study in Norway where onset was defined by reports from physicians based on interactions with parents or patients; and in that study the median time from vaccination to onset was eleven weeks, with forty-two of the fifty-eight patients experiencing clinical symptoms within six months of vaccination. (*Id.* (citing Heier et al., *Incidence of narcolepsy in Norwegian children and adolescents after vaccination against H1N1*

influenza A, 14 SLEEP MEDICINE 867-871 (2013) (Ex. JJ)).) Dr. Deak notes that this study found "no significant difference in the incidence of narcolepsy during the second year after vaccination compared to unvaccinated children in the same time period." (*Id.*) In light of these studies, Dr. Deak "[do[es] not agree that causation can be inferred with a greater than one year time interval between vaccination and the development of symptoms in H1N1." (*Id.*)

Nor does Dr. Deak believe that the HPV vaccine is analogous to the H1N1 vaccine. (Ex. GG, p. 3.) She emphasizes that there is no literature demonstrating an increased incidence of narcolepsy with the HPV vaccine administered in this case. (*Id.*) Dr. Deak disagrees with Dr. Steinman's claim that results that are not statistically significant are still consistent with "a greater than 50% likelihood" that there is a relationship between HPV vaccination and development of narcolepsy. (*Id.*) Dr. Deak stresses that without a significant association, reviewing experts cannot determine whether there is any difference in narcolepsy incidence between unvaccinated and vaccinated individuals in this study. (*Id.*)

f. Dr. Whitton's first supplemental report, Exhibit EE

In his first supplemental report, Dr. Whitton echoes Dr. Deak's opinions on the Arnheim-Dahlstrom et al. study. (Ex. EE, pp. 1-2.) Dr. Whitton observes that the authors in the Arnheim-Dahlstrom study did not provide the actual p value of their findings regarding narcolepsy, but only state that there was no significant association between vaccinated and unvaccinated groups. (*Id.* at 2.) Thus, Dr. Whitton explains, Dr. Steinman's inference regarding "95% certainty" is unjustified. (*Id.*) Dr. Whitton also notes a more recent study in which the authors again studied the frequency of narcolepsy following HPV vaccination and "again, no significant association between the two was identified." (*Id.* (citing Hvid, et al., *Human papillomavirus vaccination of adult women and risk of autoimmune and neurological diseases,* 283 J. Intern. Med. 154-165 (2018) (Ex. FF)).)

Dr. Whitton also seeks to further refute the significance of Dr. Steinman's positive and negative BLAST searches. (Ex. EE, pp. 2-3.) Dr. Whitton explains that Dr. Steinman's "negative searches" are BLAST searches which failed to identify a homology within an acceptable degree (per Dr. Steinman's criteria, 5/12 amino acids). (*Id.* at 3.) However, Dr. Whitton notes that when he replicated the same "negative" BLAST search, comparing the same two proteins, hypocretin and the L1 protein of HPV18, he identified thirteen homologies of 5/12 or better. (*Id.*) Dr. Whitton also replicated the "negative" BLAST search for HPV16 and identified nine homologies of 5/12 or better. (*Id.*) These results, Dr. Whitton explains, again demonstrate that homologies are commonplace. (*Id.*)

Like Dr. Steinman, Dr. Whitton agrees that there are "many perfect matches" between the two HPV L1 proteins and that "such similarities 'are expected.'" (Ex. EE, p. 4.) Yet Dr. Whitton suggests that the question that remains unanswered is, why then, despite the presence of so many similarities, do these proteins not induce cross-

protective immune responses? (*Id.*) Again Dr. Whitton explains that despite the 487 homologies, the L1 protein of HPV6 does not protect against HPV11, and vice-versa. (*Id.*) Thus, no biologically-relevant cross-reactivity is induced by the HPV vaccine, even in the presence of alum as Dr. Steinman suggests. (*Id.*) According to Dr. Whitton, Dr. Steinman also provides no evidence that these suspected immune responses would be harmful. (*Id.*)

g. Dr. Steinman's second supplemental report, Exhibit 43

In his second supplemental report, Dr. Steinman emphasizes that his molecular mimicry theory demonstrates how a vaccine could cause the claimed injury; the theory is "not based on 'certainty,' and thus never intended to 'surely be biologically-significant.'" (Ex. 43, p. 1.) Dr. Steinman cites the Latorre et al. study which he suggests confirms his "smoking gun." (Ex. 43, p. 2; Latorre et al., *T cells in patients with narcolepsy target self-antigens of hypocretin neurons,* 562 NATURE 63 (2018) (Ex. 45).) Dr. Steinman highlights results which discovered a T cell that responded to the sequence MGRRAGAEPAPRP in the spinal fluid of a patient with narcolepsy. (*Id.* at 3.) This cytotoxic T cell, Dr. Steinman concludes, "would have the capacity to target and kill hypocretin neurons." (*Id.*)

Dr. Steinman further remarks that the BLAST searches with hypocretin did not identify a large number of epitopes. (Ex. 43, p. 5.) For HPV11 Dr. Steinman reports only one region of hypocretin (a 5/10 sequence) and for HPV6 Dr. Steinman reports three regions were identified but only the 5/10 sequence was identified as causing experimental neuroinflammation. (*Id.*) The other two sequences were considered "not to be 'of interest.'" (*Id.*) According to Dr. Steinman, the "confirmation with actual experimental data" from LaTorre indicates that the BLAST search efforts "are fruitful and that they can definitively identify a mimic in the HPV vaccine with orexin." (*Id.*)

Dr. Steinman also suggests that Dr. Whitton may not have used the alignment algorithms of BLAST, possibly explaining the differences in their BLAST results. (Ex. 43, p. 5-8.) Given that the HPV vaccine contains a molecular mimic identified as a target of killer T cells found in the spinal cord of narcolepsy patients, Dr. Steinman disagrees with Dr. Deak's conclusion that no causal relationship can be found. (*Id.* at 9.) Dr. Steinman also opines that if an individual, such as petitioner, receives an HPV vaccine that "'boosts' immunity to orexin, even during the early onset of narcolepsy" the vaccine could aggravate the pathologic immune response, culminating in "full blown narcolepsy." (*Id.*) Dr. Steinman reiterates his conclusions regarding the studies from Sweden, Norway, and England; but adds that the findings from the Latorre et al. study also support his conclusion that the administration of the HPV vaccine "could exacerbate incipient narcolepsy and renders the studies cited by Dr. Deak on Pandremix far less significant." (*Id*. at 9-10.)

h. Dr. Whitton's second supplemental report, Exhibit KK

In his second supplemental report, Dr. Whitton stresses that "BLAST [searches] trade[] accuracy for speed." (Ex. KK, p. 5.) Dr. Whitton asserts that his own sliding

window searches "do not have any such tradeoff." (*Id.*) Rather, Dr. Whitton claims his searches "accurately identify all instances of the sought-after homologies (e.g., 5 identities out of 12 resides), and they are by far the best way by which to identify short homologies." (*Id.*)

Dr. Whitton questions Dr. Steinman's methodology because Dr. Steinman's smoking gun (RAGAEPAPRP) falls short of the Silvanovich et al. standard, which Steinman relies upon in his own report. (Ex. KK, p. 6; Ex. 43, pp. 4-5.) The Silvanovich standard requires "(i) a window of at least 80 amino acids in length (ii) in which there is at least 35% amino acid identity and (iii) whose E-value[20] must be lower than 3.9 x $^{10-7}$." (*Id.* at 7 (citing Silvanovich et al., *The value of short amino acid sequence matches for production of protein allergenicity,* 90 TOXICOL. SCI. 252-258 (2006) (Ex. OO); Silvanovich et al., *The use of E-scores to determine the quality of protein alignments* 54 REGUL. TOXICOL. PHARMACOL. S26 (2009) (Ex. PP)).) According to Dr. Whitton, none of Dr. Steinman's BLAST results meet these criteria. (*Id.* at 6.) Moreover, a BLAST result that meets the three Silvanovich criteria, "**may** provide a hint about the overall shape of a protein" and "**may** provide a hint about IgE responses, but it can tell us absolutely nothing about whether or not that sequence may trigger a T cell response." (Ex. KK, p. 8) (emphasis in original).

According to Dr. Whitton, Dr. Steinman's "chance finding" (RAGAEPAPRP) did not predict the observations later made by Latorre et al. (Ex. KK, p. 12.) Dr. Whitton frames Dr. Steinman's theory as follows: "if 'vaccine X' contains a homology to Latorre's 20 amino acid peptide, then that vaccine more likely than not causes narcolepsy." (*Id.*) To test the validity of Dr. Steinman's theory, Dr. Whitton compared the short orexin sequence against the measles vaccine. (Ex. KK, pp. 14-15.) Dr. Whitton identified four homologies, and then carried out the same comparison using BLAST, and one hit was returned, containing a 5/11 homology with an E-value of 0.17. (*Id.* at 15.) Dr. Whitton explains that these results indicate that the measles vaccine, more likely than not, triggers narcolepsy. (*Id.*) Yet, "[t]he MMR vaccine was introduced in 1963" and "no association has ever been reported between MMR and narcolepsy." (*Id.*) The mere existence of a homology to the orexin sequence, therefore, does not "inculpate[] a vaccine." (*Id.*)

Dr. Whitton also remarks that narcolepsy and orexin deficiency are commonly associated with MHC class II, which tends to impact $CD4^+$ T cells (not $CD8^+$ T cells). (Ex. KK, p. 15.) Dr. Steinman notes in his report that petitioner carries the class II MHC allele. (*Id.* (citing Ex. 14, p. 6.) However, Dr. Steinman's smoking gun responds to an epitope that is presented by MHC class I (stimulating $CD8^+$ T cells), not by MHC class II. (*Id.*) Moreover, Dr. Whitton concludes that there is no evidence that that the orexin-peptide-responsive $CD8^+$ T cells are the cause of the disease. (*Id.*) Instead, they could

[20] The Expect value € is "a parameter that describes the number of hits one can "'expect' to see by chance when searching a database of ap articular size." (Ex. KK, p. 6.) *See* https://blast.ncbi.nlm.nih.gov/Blast.cgi?CMD=Web&PAGE_TYPE=BlastDocs&DOC_TYPE=FAQ#expect (last visited Sept. 1, 2021).

"well be the **result** of the disease; perhaps orexin released from damaged neurons has induced these cells." (*Id.*) (emphasis in original.)

i. Dr. Steinman's third supplemental report, Exhibit 49

In his third supplemental report, Dr. Steinman opines that Dr. Whitton's analysis "'conveniently ignore[s]' a key amino acid or series of key amino acids." (Ex. 49, p. 4.) According to Dr. Steinman, Table 1 in Exhibit KK does not show whether the smoking gun (RAGAEPAPRP) by itself would stimulate the clone found in the spinal fluid of a narcolepsy patient because Dr. Whitton's table lacks the terminal amino P. (*Id.* (citing Sakai et al, *Involvement of distinct murine T-cell receptors in the autoimmune encephalitogenic response to nested epitopes of myeline basic protein,* 85 PROC. NATL. ACAD. SCI. USA 8608-8612 (1988) (Ex. 51)).) Without one or more critical amino acids, Dr. Steinman stresses that Dr. Whitton's analysis is "deeply flawed." (Ex. 49, p. 4.)

Dr. Steinman also summarizes his search process in detail, at the request of Dr. Whitton. (Ex. 49 pp. 5-8 (*see* Ex. KK, p. 7 n. J.) Dr. Steinman adds two additional steps beyond the BLAST searches and explains that this filtration "eliminates sequences homologies that are below a threshold that has been shown to induce neuroinflammation." (Ex. 49, p. 5.) Finally, Dr. Steinman adds a third filter "using the LaTorre paper" and the Immune Epitope Database (IEDB).[21] (*Id.*)

j. Dr. Whitton's final supplemental report, Exhibit RR

In his final supplemental report, Dr. Whitton likewise agrees that removing a single amino acid can alter how a peptide is "seen" by a $CD8^+$ T cell. (Ex. RR, p. 4.) However, Dr. Whitton suggests that Dr. Steinman's "missing proline" argument is flawed. (*Id.* at 5.) A peptide that does not trigger $CD8^+$ T cells does not transform into a peptide that can stimulate $CD8^+$ T cells simply by the addition of an amino acid. (*Id.*) According to Dr. Whitton, the opposite is true. (*Id.*) The proper method is to "identify a peptide that can stimulate T cells, and then [] remove peptides from either side, until you identify the minimal number of peptides that can still activate the T cells" – known as the minimal epitope. (*Id.*) (emphasis in original).

Dr. Whitton remarks that Dr. Steinman's smoking gun is in fact "an empty barrel." (Ex. RR, p. 6.) He explains that peptide 13 is recognized by the $CD8^+$ T cells, while peptide 12 is not. (*Id.*) From this, Dr. Whitton opines, it is possible to conclude that the T cells respond to peptide 13 because there are an additional 8 amino acids at the right-hand end. (*Id.*) It is unclear, however, how many of those 8 amino acids are needed to trigger the T cells. (*Id.*) Yet, by looking at peptide 14, which the T cells also recognize, Dr. Whitton opines that it is possible to discard half of the smoking gun peptide without

[21] The IEDB "catalogs experimental data on antibody and T cell epitopes studied in humans, non-human primates, and other animal species in the context of infectious disease, allergy, autoimmunity, and transplantation. The IEDB also hosts tools to assist in the prediction and analysis of epitopes." *See* https://www.iedb.org/home_v3.php (last visited Sept. 1, 2021).

preventing T cell recognition. (*Id.*) Ultimately, of the remaining half, only 2 residues are identical between HPV L1 and orexin. (*Id.* at 7.)

Dr. Whitton agrees that the IEDB database is a valuable resource. (Ex. RR, p. 8.) According to Dr. Whitton, however, Dr. Steinman should have entered the vaccine part of the homology in the IEDB database, not the sequences from the human protein orexin. (*Id.* (citing Ex. 49, p. 7).) After entering Dr. Steinman's homology into the IEDB, Dr. Whitton reports that no match was found. (Ex. RR, p. 8.) Therefore, Dr. Whitton concludes, Dr. Steinman's homology in the HPV L1 protein is not known to be an immunological epitope. (*Id.*)

k. Dr. Steinman's final supplemental report, Exhibit 55

In his final supplemental report, Dr. Steinman reiterates that the epitope RAGAEPAPRP from the BLAST search is contained in the epitope targeted by a $CD8^+$ T cell in the spinal fluid of a patient with narcolepsy. (Ex. 55, p. 2.) Dr. Steinman maintains his conclusion that "[t]here ***is*** a component of the vaccine that is a molecular mimic of the orexin molecule targeted in narcolepsy." (*Id.*) (emphasis in original). Dr. Steinman also opines that the molecular mimics, along with the adjuvant in the vaccine "could become problematic in a susceptible individual, triggering narcolepsy cataplexy syndrome in [petitioner]." (*Id.* at 3.)

V. Party Positions

a. Petitioner's contentions

Petitioner contends that the record evidence is clear in demonstrating that petitioner's May 1, 2013 HPV vaccination significantly aggravated the disease process of narcolepsy. (ECF No. 73, p.1.) Petitioner asserts that, consistent with narcolepsy, she experienced sleeplessness beginning in early April 2013, but the increase and evolution of her symptoms were ultimately caused by the HPV vaccine. (*Id.* at 13-16.)

Petitioner asserts that her diagnosis of narcolepsy is not in controversy. (*Id.* at 7.) Petitioner contends that the medical records clearly indicate that petitioner was an otherwise healthy child, with no complaints of neurological problems. (*Id.* at 17.) Ten days after her vaccination, petitioner asserts that she presented to the hospital with new and worsening symptoms including slurred speech, weakness, difficulty walking, muscle twitching and significantly worsened sleep. (*Id.*) Dr. Steinman's molecular mimicry theory links the vaccination to petitioner's subsequent significant aggravation, resulting in her diagnosis of narcolepsy. (*Id.* at 19.)

Petitioner acknowledges that the results discussed in Court Exhibit 1 were not statistically significant, nor did the authors provide the actual p value. (ECF No. 73, p. 24.) Petitioner contends that the rise in cases of narcolepsy in the unvaccinated group, however, is evidence supporting the plausibility that petitioner's HPV vaccine could significantly aggravate her narcolepsy. (*Id.*) Petitioner also acknowledges some

variability in the recorded patient histories, but maintains that prior to her HPV vaccination, petitioner only suffered awakenings at night accompanied by daytime sleepiness. (*Id.* at 26.) Petitioner asserts that "[t]here is no evidence of another factor that may have exacerbated [petitioner's] narcolepsy." (*Id.* at 26-27.)

In response to respondent's contentions, petitioner stresses that there is evidence in the contemporaneous records that petitioner's symptoms dramatically increased ten days after her vaccination. (ECF No. 76, p. 2.) Petitioner also stresses that respondent's reliance on the Trost et al. study is inappropriate. (*Id.* at 6.) Petitioner argues that this study focuses on bacterial sequences, as opposed to viral proteins. (*Id.*) In addition, petitioner contends that Dr. Steinman's theory presents a causal link between the HPV vaccine and narcolepsy based on T cell pathology, not antibody-mediated dysfunction. (*Id.* at 7-8.) Petitioner emphasizes that the Pandemrix studies were cited by Dr. Steinman to show a correlation of timing, not to draw comparisons between the HPV and H1N1 vaccines. (*Id.* at 9.)

b. Respondent's contentions

Respondent argues that Dr. Steinman employs an unreliable methodology and does not cogently explain how the HPV vaccine may cause or significantly aggravate narcolepsy through molecular mimicry. (ECF No. 75, pp. 17-18.) Respondent also stresses that petitioner's treating physicians do not support vaccine-causation, noting that her neurologist noted daytime sleepiness, cataplexy and sleep paralysis were "exacerbated after Gardasil shot." (*Id.* at 18, 31.) Respondent argues this observation only amounts to a temporal association. (*Id.*) Respondent further alleges that petitioner's reliance on epidemiological studies involving the Pandemrix H1N1 influenza vaccine is unpersuasive. (*Id.* at 36.)

Respondent also contends that petitioner's symptoms followed a typical course of pediatric narcolepsy, and her symptoms were already progressing prior to vaccination. (ECF No. 75, pp. 36-37.) Respondent stresses that petitioner overlooks the fact that she has two "diagnostic markers" of narcolepsy, low levels of hypocretin in her spinal fluid and the HLA DQB1*0602 gene. (*Id.* at 38.) Respondent contends that pediatric narcolepsy diagnoses are often delayed, and the timing of petitioner's diagnosis "says nothing about the actual course of her disease." (*Id.*) Finally, respondent argues that any "substantial factor" claim would suffer the same limitations with respect to establishing vaccine causation. (*Id.* at 41-42.)

VI. Discussion

The most extensively debated aspect of this case is the validity of petitioner's theory of causation explaining how petitioner's HPV vaccine could have significantly aggravated her condition. This presents a threshold issue in this case. Accordingly, I will address petitioner's theory of causation first. Having found that petitioner did not meet her burden of proof on this point, I will then more briefly address the remaining elements of the six-part *Loving* test discussed above.

a. Petitioner's Medical Theory (*i.e.* the *Althen* prong one / *Loving* prong four)

Petitioner's burden under the first *Althen* prong/fourth *Loving* prong is to provide, by preponderant evidence, "a medical theory causally connecting the vaccination and the injury." *Althen,* 418 F.3d at 1278. Such a theory must only be "legally probable, not medically or scientifically certain." *Knudsen v. Sec'y of Human & Health Servs.*, 35 F.3d 543, 548-49 (Fed. Cir. 1994). Moreover, scientific evidence offered to establish *Althen* prong one is viewed "not through the lens of the laboratorian, but instead from the vantage point of the Vaccine Act's preponderant evidence standard." *Andreu v. Sec'y of Health & Human Servs.*, 569 F.3d 1367, 1380 (Fed. Cir. 2009). However, to satisfy this prong, petitioner's theory must be based on a "sound and reliable medical or scientific explanation." *Knudsen*, 35 F.3d at 548; *Boatmon*, 941 F.3d at 1359.

Petitioner's medical theory regarding how her HPV vaccination significantly aggravated her narcolepsy cataplexy syndrome posits an autoimmune response to the vaccination, "targeting human proteins that are implicated in the disease process of narcolepsy." (ECF No. 73, p. 19.) Petitioner relies on Dr. Steinman's theory of molecular mimicry to link the vaccination to her subsequent significant aggravation of narcolepsy. (*Id.*) Below I shall address (1) the debate as to whether narcolepsy is an autoimmune condition and whether a relevant autoantibody has been identified; (2) whether the epidemiologic evidence links narcolepsy to the HPV vaccine by preponderant evidence; and (3) whether Dr. Steinman's demonstrated homologies can be shown to demonstrate a causal relationship between the HPV vaccine and injury.

i. Narcolepsy Type 1 and autoimmunity

Narcolepsy type 1 is a disorder characterized by excessive daytime sleepiness and signs of REM-sleep dissociation, the most specific of which is cataplexy. (American Academy of Sleep Medicine, *Narcolepsy Type 1,* International Classification of Sleep Disorders (3d ed. 2014) (Ex. F).) Narcolepsy is caused by hypocretin deficiency, likely due to the selective loss of hypocretin-producing neurons in the hypothalamus. (Mignot, *supra,* at Ex. O.) According to Mignot, when cataplexy is present, "the cause is almost always an immune-mediated destruction of the hypocretin-producing (also called orexin) neurons in the hypothalamus." (*Id.*) The autoimmune hypothesis is the leading theory for narcolepsy type 1, due to a strong association between narcolepsy type 1 and the human leukocyte antigen (HLA) DQB1*0602. (Postiglione, *supra,* at 70 (Ex. K).)

Respondent's expert, Dr. Deak, acknowledges that the autoimmune hypothesis is the leading theory for the pathophysiology of narcolepsy type 1, but stresses that "autoantibodies specific to hypocretin peptides have not been found," and that direct evidence supporting the autoimmune hypothesis is lacking. (Ex. A, p. 6.) Instead, she notes that (i) seasonal differences in narcolepsy incidence, (ii) the rise in incidences post 2009-2010 administration of the AS03-adjuvanted H1N1 vaccine and (iii) the association with anti-streptococcal antibodies, all circumstantially support the theory that

environmental factors contribute to the development of narcolepsy in patients who are genetically susceptible. (Ex. A, p. 6 (citing Postiglione et al., *supra,* at Ex. K).)

In that regard, Dr. Steinman notes three groups[22] who have "reported immune responses to hypocretin reception 2 in narcolepsy": (i) a group led by Dr. Steinman who found that "in vaccine-induced narcolepsy, there are antibodies to HCRT-R2" and who identified a region of the HCRT-R2 molecule located at the site where hypocretin binds the receptor[23] (ii) a group in Japan which found antibodies to HCRT-R2 in narcolepsy[24] and (iii) as did a group from Oxford.[25] (Ex. 14, p. 10.) Upon examination, these three studies do not preponderantly establish HCRTR2 antibodies as the cause of narcolepsy.

Tanaka et al. developed a study testing serum from one-hundred eighty-one patients with narcolepsy, ten patients with other hypersomnia and ninety-one control subjects. (Tanaka et al., *supra,* at 634 (Ex. 29).) As a result, they observed autoantibodies against hypocretin in nine narcolepsy patients, HCRTR in three patients, HCRTR1 in one patient, and HCRTR2 in five patients. (*Id.* at 635.) Eight of these

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[22] As noted above, Dr. Steinman also mentions a fourth group, Mignot's group, who showed "some evidence of antibodies to HCRT-R2 in narcolepsy" post Pandemrix vaccination, though he discounts these findings due to a "major flaw" in one of the assays for HCRT-R2 that appears in their supplementary data. (*Id.* (citing De la Herrán-Arita et al., *supra* at Ex. 25; De la Herrán-Arita et al., *supra* at Ex. 26 (Retraction published on July 30, 2014)).) In the De la Herrán-Arita et al. study (2013) ("Mignot's group") researchers tested for the presence of T cell reactivity toward HCRT epitopes $HCRT_{56-68}$ and $HCRT_{87-99}$. (De la Herrán-Arita, *supra,* at Ex. 25, p. 7-9.) The results indicated that $CD4^+$ T cells reactive to the presentation of $HCRT_{56-68}$ and/or $HCRT_{87-99}$ by DQ0602 were present in most patients with narcolepsy. (*Id.* at 7.) The autoantigens primarily elicited a T_H1 response, which the authors explain is "characteristic of many autoimmune diseases." (*Id.*) Yet, these results were later retracted. (De la Herrán-Arita, *supra,* at Ex. 26, p. 14.) In a later article, Mignot explained that the hypocretin cell loss in narcolepsy and the presence of the HLA DQB1*0602 is what "rekindled the hypothesis of autoimmunity," with hypocretin as the logical target. (Mignot, *supra,* at Ex. O, p. 865.) Despite this association, "[s]uprisingly, however, autoantibodies targeting hypocretin peptides have not been found, and immune staining of hypothalamic tissue with human narcolepsy sera has not revealed autoantibodies target colocalized antigens on these neurons." (*Id.*) Passive transfer experiments of human sera in mice have been published, which suggested the presence of functional autoantibodies, however, Mignot explains that these studies could not be replicated. (*Id.*) After the results of De la Herrán-Arita et al. study (2013), researchers felt "a blood test for narcolepsy might be close at hand, but on finding these data were invalid, [the authors] withdrew the paper." (*Id.* at 866.) Ultimately, Mignot suggests that there is strong circumstantial evidence supporting an autoimmune hypothesis though direct evidence is lacking. (*Id.*)

[23] Ahmed et al., *Antibodies to influenza nucleoprotein cross-react with human hypocretin receptor 2,*7 (294) SCI. TRANSL. MED. (2015) (Ex. 27). Dr. Steinman notes that his group identified the region of the HCRT-R2 molecule that was previously identified at the University of Texas Southwestern Medical School, "precisely at the site where hypocretin binds the receptor." (Ex. 14, p. 10) (citing Yin et al, *Structure and ligand-binding mechanism of the human OX1 and OX2 orexin receptions,* 23(4) NAT. STRUCT. MOL. BIOL. 293-9 (2016)).)

[24] Tanaka et al., *Detection of autoantibodies against hypocretin, hcrtr1, and hcrtr2 in narcolepsy: anti-hcrt system antibody in narcolepsy,* 29(5) SLEEP 633-638 (2006) (Ex. 29).

[25] Giannocarro et al, *Antibodies against HCRT-R2 are rare in narcolepsy,* 40(2) SLEEP (2017) (Ex. 30.)

patients had anti-HCRT neurotransmission system antibodies, with one patient having positive reactions against both HCRTR1 and 2. (*Id.*) However, positive reactions were also noted against HCRTR1 in two control subjects and HCRTR2 in one control subject. (*Id.* at 636.) Tanaka et al. indicated that "[anti-HCRT antibodies] might be naturally occurring autoantibodies without pathologic function or might not cross the blood-brain barrier to cause narcolepsy." (*Id.* at 637.) The authors observed that no relationships existed between these autoantibodies and HLA DRB1*1501/DRQB1*0602 haplotypes, the presence of cataplexy, the presence of subjective nocturnal sleep disruption, or the scores on the Epworth Sleepiness Scale. (*Id.*) Ultimately, their results do not support the hypothesis that autoantibody-mediated dysfunction in the hypocretin system underlies the pathophysiology of narcolepsy. (*Id.*)

The Ahmed et al. study suggested a possible link between the Pandemrix vaccine (an adjuvanted, influenza pandemic vaccine) and the development of antibodies between hypocretin receptors. (Ahmed et al., *supra,* at 1 (Ex. 27).) In that study, Dr. Steinman and his colleagues hypothesized that differences in the nucleoprotein make-up of vaccines could explain why an increased incidence of narcolepsy was observed following one type of influenza vaccine, Pandemrix, but not a differently manufactured influenza pandemic vaccine, Focetria. (*Id.*) Differences between the protein sequences from A(H1N1) pdm09 virus and the Pandemrix and Focetria vaccines identified an influenza nucleoprotein peptide similar to human HCRT receptor 2. (*Id.* at 2.) Antibodies were detected in the blood sera of higher numbers of Pandemrix-vaccinated participants with narcolepsy than with individuals who did not suffer from narcolepsy. (*Id.*) Key to this study was the authors' comparison of the nucleoprotein antibody content found in individuals who received eight different inactivated flu vaccines, in addition to three monovalent A(H1N1) pmd09 vaccines (a group which included Pandemrix). (*Id.* at 4.) Of the three monovalent vaccines, Focetria had 72.7 percent fewer nucleoproteins than Pandemrix. (*Id.*) This suggested "the possibility that lower [nucleoprotein] concentrations in Focetria could have attenuated both the immune response to nucleoprotein and the subsequent generation of [nucleoprotein] antibodies capable of cross-reactivity with HCRT receptor 2." (*Id.*) Ahmed et al. do not propose an explanation for this difference, other than to say that the vaccines were manufactured differently. (*Id.* at 1.)

In the third group cited by Dr. Steinman, Giannocarro et al. (2017), sera from fifty narcolepsy type 1 patients and eleven narcolepsy type 2 patients, twenty-two patients with other sleep disorders, fifteen health controls, and ninety-three disease controls were tested for the HCRTR2 antibodies. (Giannocarro et al., *supra,* at 1 (Ex. 30).) Using a live cell-based assay approach, the researchers found only three narcolepsy patients had IgG antibodies to HCRTR2. (*Id.* at 4-5.) They further observed that the titers were low in all three patients and no HCRTR2 antibodies were found in their CSF. (*Id.* at 5.) The authors note the earlier study from Tanaka et al., which also found a low proportion of patients with antibodies immunoprecipitating HCRTR2. (*Id.*) Taken together, Giannocarro et al. conclude that antibodies to HCRTR2 in patients with idiopathic narcolepsy "appear to be rare." (*Id.*) The results of both studies, as well as the low titers in the serum and the absence of CSF antibodies (which are usually

present in patients with typical antibody-mediated diseases) suggests that these antibodies "may not be clinically relevant." (*Id.*) However, the authors note that their results, as well as Tanaka et al., contrast with the results from Ahmed et al. (*Id.*) Giannocarro et al. suggest that their results could reflect different methodologies. (*Id.*) Moreover, they acknowledge that their three positive results were atypical because one patient presented with narcolepsy type 1 and psychosis, and two patients were DQB1*602 negative. (*Id.*) Ultimately, however, they suggest that the significance of any HCRTR2 antibodies, even in a subset of narcolepsy patients, should be interpreted with caution.

The proposition that narcolepsy may be "an immune-mediated condition is fairly well-established" in the Program. *McCollum v. Sec'y of Health & Human Servs.,* No. 14-790V, 2017 WL 5386613, at *16 (Fed. Cl. Spec. Mstr. Sept. 15, 2017), *review denied*, 135 Fed. Cl. 735 (2017), *aff'd,* 760 Fed. Appx. 1003 (2019). Other prior decisions have observed the likelihood that narcolepsy is autoimmune. *See D'Tiole v. Sec'y of Health & Human Servs.,* No. 15-085V, 2016 WL 7664475 (Fed. Cl. Spec. Mstr. Nov. 28, 2016), *review denied, decision aff'd,* 132 Fed. Cl. 421 (2017), *aff'd,* 726 F. App'x 809 (Fed. Cir. 2018); *Dougherty v. Sec'y of Health & Human Servs.,* No. 15-1333V, 2018 WL 3989519, at *43 (Fed. Cl. Spec. Mstr. July 5, 2018), *aff'd*, 141 Fed. Cl. 223 (2018); *E.S v. Sec'y of Health & Human Servs*., No. 17-480V, 2020 WL 9076620, at *44 (Fed. Cl. Spec. Mstr. Nov. 13, 2020). Here, although petitioner has preponderantly established that narcolepsy is likely an autoimmune condition, she has not preponderantly established a causal role for HCRTR2 autoantibodies in the development of the condition.

ii. Epidemiological Evidence

Even in the absence of an identified autoantibody, an epidemiological association between narcolepsy and the HPV vaccination could still potentially support a causal theory. Here again, however, epidemiological evidence showing a causal link between the HPV vaccine and the onset of narcolepsy, or in petitioner's case, significant aggravation, is also absent from this case. As a general matter, it is true that petitioners in the Vaccine Program are not required to present epidemiological evidence to establish their causation burden under *Althen. Moberly v. Sec'y of Health & Hum. Servs*., 592 F.3d 1315, 1325 (Fed. Cir. 2010). However, "[n]othing in *Althen* or *Capizzano* requires the Special Master to ignore probative epidemiological evidence that undermines petitioner's theory." *D'Tiole*, 726 F. App'x at 811 (citing *Andreu*, 569 F.3d at 1379 ("Although *Althen* and *Capizzano* make clear that a claimant need not produce medical literature or epidemiological evidence to establish causation under the Vaccine Act, *where such evidence is submitted*, the Special Master can consider it in reaching an informed judgment as to whether a particular vaccination likely caused a particular injury." (emphasis added)); *Grant v. Sec'y of Health & Human Servs.*, 956 F.2d 1144, 1148-49 (Fed. Cir. 1992) (considering negative epidemiological studies).

Partinen et al. (2012) focused on an outbreak of narcolepsy among children in Finland in 2010. (Partinen et al., *supra* at 1 (Ex. 38).) The authors speculated whether

the cause of narcolepsy was attributable to adjuvants in the Pandemrix vaccine, or some other environmental factors or genetic predisposition. (*Id.* at 7-8.) Between 2002 and 2009, 335 cases of narcolepsy (all ages) were diagnosed in Finland. (*Id.* at 4.) In 2010, 54 children were diagnosed with narcolepsy, a 17-fold increase. (*Id.* at 5.) Based on patient records, the authors placed onset of excessive daytime sleepiness at 0-242 days after receiving the H1N1 vaccine (Pandemrix, GSK). (*Id.*) Yet the authors stressed the fact that the Pandemrix flu vaccine was the *only* form of the vaccine associated with an increased incidence of narcolepsy. (*Id.* at 7) ("there is no evidence of an increased risk of narcolepsy with any other vaccine than the AS03 adjuvanted Pandemrix").

Winstone et al. (2014) sought to investigate the onset of narcolepsy among English children who received the AS03 adjuvanted pandemic A/H1N1 2009 vaccine (Pandemrix). (Winstone, *supra,* at 1 (Ex. 39).) The authors identified seventy-five patients with narcolepsy, though only eleven received the Pandemrix vaccine before narcolepsy onset, a "relatively small number." (*Id.* at 1.) As Dr. Steinman points out, among the eleven patients who received the Pandemrix vaccine: six patients reported onset of narcolepsy within three months, one patient reported onset between four and six months, and four patients reported onset between seven and fourteen months. (*Id.* at 4.) However, the authors acknowledged that the small number of patients who in fact received the Pandemrix vaccine reduces the likelihood of finding statistically significant differences between vaccinated and unvaccinated patients. (*Id.* at 8.)

Szakacs et al. (2013) designed a retrospective study conducted in Sweden where symptom onset was determined based on medical record review and telephone interviews with parents and patients. (Szakacs et al., *supra,* at Ex. II).) In that study, the median time from H1N1 vaccination to symptom onset was nine-and-a-half weeks, with nineteen of the twenty-eight patients developing symptoms in twelve weeks or less. (*Id.* at 1315.) In addition, Heier et al. (2013) conducted a study in Norway where onset was defined by reports from physicians, based on interactions with parents or patients; and in that study the median time from vaccination to onset was eleven weeks, with forty-two of the fifty-eight patients experiencing clinical symptoms within six months of vaccination. (Heier et al., *supra,* at Ex. JJ.) The authors, however, found no significant difference in the incidence of narcolepsy during the second year after vaccination compared to unvaccinated children in the same time period. (*Id.* at 868)

The literature cited by Drs. Deak and Steinman, discussed above, demonstrates an increased incidence of narcolepsy after the administration of the AS03-adjuvanted H1N1 vaccine in several European countries. Yet, there is no increased risk of narcolepsy with either H1N1 vaccines that contained other adjuvants, such as Focetria, or among non-adjuvanted H1N1 vaccines given in the United States. (Partinen, *supra,* at Ex. E; Duffy et al., *supra,* at Ex. Q; Nguyen et al., *supra,* at Ex. R.)

Gardasil, in this case the quadrivalent vaccine, is prepared from four Human Papillomavirus type-specific virus-like particles (VLPs) from the L1 proteins of HPV 6, 11, 16, and 18, and is entirely unrelated to the above-discussed vaccines. In contrast to

the above, the epidemiological study by Arnheim-Dahlstrom (2013) introduced into the record by Special Master Millman, "show[ed] that among almost one million adolescent girls, [the] HPV vaccine was not [r]elated causally to narcolepsy." (ECF No. 26.) This population-based study included all adolescent girls aged between 10 and 17 years in Denmark and Sweden who received the quadrivalent HPV vaccine between 2006 and 2010. (Arnheim-Dahlstrom et al., *supra,* at 2 (ECF No. 26-1) (Court Ex. 1).) The incidence rate for immunized subjects in this study was 2.61 incidents of narcolepsy per 100,000 person years whereas the unvaccinated rate was 1.81 per 100,000 person years. (*Id.* at 8.) The authors concluded that there was no significant association between the HPV quadrivalent vaccine and narcolepsy. (*Id.* at 5, 8.)

In Dr. Steinman's interpretation of this study, he concludes that the Gardasil vaccine is associated with a higher rate of narcolepsy compared to the unvaccinated, "even though it may not reach so-called 'statistical significance.'" (Ex. 14, p. 31.) In contrast, Dr. Whitton stresses that the authors do not provide the actual p value[26] of their findings regarding narcolepsy. (Ex. EE, p. 2; ECF No. 26-1, p. 5.) In my review, I note that Table 2 of the study expresses a confidence interval of 95 percent for the incidence rate for both unvaccinated and vaccinated groups showing that the lower confidence limit for the incidence rate of narcolepsy among the vaccinated group (1.17) is lower than the lower confidence limit for the unvaccinated group (1.34).[27] Thus, this data does not even express confidence that the actual incidence rate is higher among the vaccinated group at all. (ECF No. 26-1, p. 8.) Although they noted the results should be viewed with caution, the authors likewise indicated that no safety signal was detected by the study. (*Id*. at 5.) Thus, I am not persuaded by Dr. Steinman's subjective impression of the difference as "impressive" despite lacking statistical significance. (Ex. 14, p. 31 ("these are large samples and the difference is impressive in my opinion…even though it may not reach so-called 'statistical significance.'") *See Thompson v. Sec'y of Health & Human Servs.,* No. 99-436V, 2003 WL 21439672, at *18 (Spec. Mstr. Fed. Cl. May 23, 2003) (observing that "professionals in the field of epidemiology rely upon statistical significance in order to reach valid, credible conclusions.")

Dr. Whitton also provides a more recent study, Hvid et al. (2018), where the authors again studied the frequency of narcolepsy following HPV vaccination and still no significant association between the two was identified. (Ex. EE, p. 2 (citing Hvid, et al., *supra,* at Ex. FF).) Like the earlier population-based study, researchers included all

[26] P value is "the probability of obtaining by chance a result at least as extreme as that observed, even when the null hypothesis is true and no real difference exists; when P ≤ 0.05 the sample results are usually deemed significant at a statistically important level and the null hypothesis rejected." *P-value,* DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=13359 (last visited Oct. 8, 2021).

[27] Confidence interval is "a type of statistical interval estimate for an unknown parameter: a range of values believed to contain the parameter, with a predetermined degree of confidence. Its endpoints are the *confidence limits,* and it has a stated probability (the *confidence coefficient*) of containing the parameter." *Confidence interval,* DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=13359 (last visited Oct. 12, 2021).

women from Denmark and Sweden who received the quadrivalent HPV vaccine between 2006-2010, only this time among women 18-44 years old. (Hvid et. al., *supra,* at 155 (Ex. FF).) Among 431 reported events of narcolepsy, the authors recorded 21 reports of narcolepsy any time after vaccination, with 10 reported within 179 days post-vaccination and 11 reported within 180 days or more. (*Id.* at 9.) These results were not highlighted as "significant associations." (*Id.*) Taken together, the Arnheim Dahlstrom et al. study and the Hvid et al. study suggest no significant association between the frequency of narcolepsy and HPV vaccination.

Dr. Deak raises a further concern that the reported timing of symptom onset is generally prone to recall bias. (Ex. GG, p. 2.) Based on her own clinical experience, and the insidious nature of narcolepsy onset, Dr. Deak stresses that the onset of symptoms in a retrospective study is likely to have occurred prior to the reported time of presentation. (*Id.*) Researchers in Hvid et al. acknowledge that "[f]or many of the included outcomes, there will be a delay between onset and diagnosis." (Hvid et al., *supra,* at 163 (Ex. FF).) For this reason, the authors included two risk periods: a 180-day period for outcomes "with little delay between onset and diagnosis" and a period following 180 days for outcomes "with a more insidious onset." (*Id.*) Even still, despite the large size of the cohort, the authors stress that "many of the included outcomes are rare and null findings should be interpreted in the context of statistical power." (*Id.*)

The fact that a relationship between the HPV vaccine and narcolepsy has not been uncovered epidemiologically is not in itself fatal to petitioner's claim. Nonetheless, review of the above demonstrates that the epidemiological evidence that does exist does not support petitioner's allegations.

iii. Dr. Steinman's Theory Regarding Molecular Mimicry

Petitioner presents the theory of molecular mimicry to "[link] the vaccination to her subsequent, significant aggravation that led to her diagnosis of narcolepsy." (ECF No. 73-1.) Petitioner contends that Dr. Steinman has demonstrated that components of the HPV vaccine present molecular mimics of hypocretin and hypocretin-2 receptor. (*Id.*) Specifically, Dr. Steinman carried out BLAST searches to identify homologies between the components of the Gardasil vaccine and various components of the hypocretin pathway, including hypocretin itself and the HCRT-R2 receptor. (Ex. 14, p. 11.)

Dr. Steinman classifies his criteria for a "meaningful molecular mimic" as a run of 5 or more of 12 amino acids that are identical. (*Id.*) Dr. Whitton, however, explains that in order to identify an amino acid sequence as a "mimic," one cannot rely on a shared homology alone. (Ex. C, p. 5.) Rather, mimicry is defined by the "immune response that the sequence induces" and to be a "mimic" the amino acid sequence must "(i) [] trigger an immune response and, (ii), that response must recognize (i.e., cross-react with) the other peptide[.]" (*Id.*) (emphasis in original). Unless both criteria are met, then it is not a mimic, but merely a homology. (*Id.*)

Indeed, "molecular mimicry is a generally accepted scientific principle, [though] mere invocation of the scientific term does not carry a petitioner's burden in a Program case." *Deshler v. Sec'y of Health & Human Servs*., No. 16-1070V, 2020 WL 4593162, at *20 (Fed. Cl. Spec. Mstr. July 1, 2020) (citing *Forrest v. Sec'y of Health & Human Servs.*, No. 14-1046V, 2019 WL 925495, at *3 (Fed. Cl. Spec. Mstr. Jan. 18, 2019)). This is because, as Dr. Whitton opines in this case, "the finding of sequence homology does not necessarily mean the similarity has significance to the immune system." *Tullio v. Sec'y of Health & Human Servs.*, No. 15-51V, 2019 WL 7580149, at *15 (Fed. Cl. Spec. Mstr. Dec. 19, 2019), *review granted, decision aff'd,* 149 Fed. Cl. 448 (2020); *see also Caredio v. Sec'y of Health & Human Servs.,* No. 17-0079V, 2021 WL 4100294, at *31 (Fed. Cl. Spec. Mstr. July 30, 2021), *review granted, decision aff'd,* __ Fed. Cl. __ (2021) ("*demonstration of homology alone is not enough to establish a preponderant causation theory*") (emphasis in original) (citing *Schultz v. Sec'y of Health & Human Servs.,* No. 16-539V, 2020 WL 1039161, at *22 n. 24 (Fed. Cl. Spec. Mstr. Jan. 24, 2020) ("[m]ere demonstration of theoretical homology alone, based on computer-driven searches involving databases of amino acid sequences, does not carry the day")).

Both Drs. Steinman and Whitton rely on the study from Silvanovich et al. (2006) in their discussions on the reliability and value of BLAST searches. It is true, as Dr. Steinman asserts, the authors concluded that "for large proteins and an expanding allergen database, a FASTA or BLAST bioinformatics search appears to be the optimum method for identifying potential similarities between newly expressed proteins and known allergens." (Silvanovich et al., *supra,* at Ex. OO.) The study performed a series of analyses to determine whether there was a scientifically justified search window size that could identify allergen sequence characteristics, in the context of genetically engineered crops. (*Id.* at 252.) Based on the results, Silvanovich et al. concluded that searches for short amino acid sequence matches of eight amino acids or fewer, used to identify proteins as potential cross-reactive allergens, "is a product of chance and adds little value to allergy assessments for newly expressed proteins." (*Id.* at 258.) These results, Dr. Whitton explains, show that Dr. Steinman's 5/12 homologies are entirely predictable. (Ex. C, p. 9.)

The "Silvanovich standard," as Dr. Whitton describes it, requires a window of at least 80 amino acids in length, in which there is at least 35% amino acid identity, and whose E-value must be lower than 3.9×10^{-7}. (Silvanovich et al., *supra,* at Ex. OO; Silvanovich et al., *supra,* at Ex. PP.) According to Dr. Whitton, none of Dr. Steinman's BLAST results meet these criteria. (Ex. KK, p. 6.) Even assuming *arguendo* that Dr. Steinman's BLAST results did meet these criteria, nothing in this article reveals whether Dr. Steinman's sequence may trigger a T cell response.

The Latorre study identified a 20 amino acid sequence in orexin that can stimulate $CD8^+$ T cells from a single narcolepsy patient's spinal fluid— which Dr. Steinman suggests confirms the BLAST searches linking the HPV vaccine and a key portion of the orexin molecule. (Latorre, *supra,* at Ex. 45, p. 5; Ex. 43, p. 2-5.) However, to challenge the validity of Dr. Steinman's theory, Dr. Whitton compared the short orexin sequence against the measles vaccine. (Ex. KK, pp. 14-15.) Dr. Whitton

identified four homologies, and then carried out the same comparison using BLAST, and one hit was returned, containing a 5/11 homology with an E-value of 0.17. (*Id.* at 15.) Dr. Whitton explains that, following Dr. Steinman's logic, these results indicate that the measles vaccine, more likely than not, triggers narcolepsy. (*Id.*) Yet, "[t]he MMR vaccine was introduced in 1963" and "no association has ever been reported between MMR and narcolepsy." (*Id.*) The mere existence of a homology to the orexin sequence, therefore, does not "inculpate[] a vaccine." (*Id.*) Accordingly, in the context of this vaccine and this injury, Dr. Steinman's finding of homology is not sufficient to establish causation.

While the demonstrated homology offered by Dr. Steinman is *potentially* useful, the scientific literature suggests that homologies are predictable and do not inevitably lead to cross-reaction. There have been instances where Dr. Steinman's use of BLAST searches has been found to help support a finding of vaccine causation. *See E.M. v. Sec'y of Health & Human Servs.,* No. 14-753V, 2021 WL 3477837, at *36-39 (Fed. Cl. Spec. Mstr. July 9, 2021) (finding persuasive Dr. Steinman's evidence of "numerous examples of sequences in the 2011 Fluarix vaccine and between earlier seasonal flu vaccines, that share similar homologies with the [protein] alpha3 nicotinic AChR, which is associated with small fiber neuropathy"); *White v. Sec'y of Health & Human Servs.,* No. 15-1521, 2019 WL 7563239, at *24 (Fed. Cl. Spec. Mstr. Dec. 19, 2019) (crediting Dr. Steinman's molecular mimicry theory and BLAST searches where there were "sufficient homologies between the basic myelin protein and two of the strains of the HPV L1 strains…and between MOG and all four HPV antigens in the vaccine[,]" which could cause TM). However, Dr. Steinman's use of BLAST search result homologies has also separately been criticized in the absence of some evidence of cross reaction as being mere uninvestigated hypothesis. *Forrest v. Sec'y of Health & Human Servs.,* No. 14-1046V, 2019 WL 925495, at *4-5 (Fed. Cl. Jan. 28, 2019) (finding that Dr. Steinman's theory that a flu vaccine caused TM via molecular mimicry was not sufficiently developed to meet Petitioner's burden under Althen prong one because Dr. Steinman had "not investigated his hypothesis[,]" other than through computerized homologies revealing "some overlap in sequences of amino acids[.]") Even where Dr. Steinman has shown in a separate context that a 5 out of 12 homology can be experimentally shown to cause disease, homology alone does not in any given instance show that a causal relationship exists between vaccine and injury.[28]

[28] Dr. Steinman relies upon animal studies in which researchers studying multiple sclerosis sought to induce paralysis in mice using mimics of myelin basic protein. Dr. Steinman derives his criteria for a "meaningful molecular mimic" from studies where scientists induced experimental allergic encephalomyelitis ("EAE") in mice using a viral peptide with homology with myelin basic protein. (*See* Ex. 14 at 11.) Similarly, Dr. Steinman cites Ufret-Vicenty et al., wherein researchers "passively transferred T cells that cross-reacted with myelin basic protein and HPV, and saw that the experimental animals became paralyzed[.]." (Ex. 14 at 26 (discussing Ex. 35)). Dr. Steinman fails to explain why these animal studies involving a different protein and a different disease are relevant to petitioner's case. *See D.G. v. Sec'y of Health & Human Servs.,* No. 11-577V, 2019 WL 2511769, at *77 (Fed. Cl. Spec. Mstr. May 24, 2019) ("[I]t [is] irrelevant that Dr. Steinman can make mice ill with inflammation of their brains and spinal cords with a mere homology of five amino acids," as "[p]etitioner is not a mouse" and "never had inflammation of her brain or spinal cord.")

In fact, as Dr. Steinman points out, the significance of the homology is informed by other areas of inquiry. (*See* Ex. 14, p. 28-29 ("[o]ther genetic and environmental factors are necessary before these self-reactive immune responses to myelin for example, or to HCRT-R2, may trigger inflammation in the brain.").) In this case, however, the other available areas of inquiry do not support a causal relationship for all the reasons discussed in the two preceding sections.

Overall, I am more persuaded by Dr. Whitton's opinion (discussed in much greater detail above) that Dr. Steinman is not in this case generating reliable evidence of molecular mimicry via his BLAST searches. Thus, I find that petitioner has not provided a medical theory causally connecting the HPV vaccine to her worsening narcolepsy, and petitioner is therefore unable to carry her burden under prong 4 of the *Loving* test. In the Vaccine Program, it is well understood that petitioners are not obligated to prove the precise mechanism as a component of their causation theory. *Kottenstette v. Sec'y of Health & Human Servs.*, No. 2020-2282, 2021 WL 2434329, at *7 (Fed. Cir. June 15, 2021); *Knudsen,* 35 F.3d at 548-59. Yet, when a mechanism is presented as the basis for petitioner's theory, it must be based on sound and reliable scientific explanation. *Boatmon*, 941 F.3d at 1359-60.

b. Significant Aggravation (*Loving* prongs one through three)

Assuming *arguendo* that petitioner did prove a medical theory demonstrating that her HPV vaccination could have caused or aggravated her narcolepsy, the remainder of the *Loving* test queries whether petitioner would be able to show that it did do so in this particular case. The threshold question in that remaining analysis is whether petitioner's condition was, in fact, significantly aggravated. To demonstrate significant aggravation, the Vaccine Act requires a "change for the worse in a preexisting condition," and "markedly greater disability, pain, or illness accompanied by substantial deterioration of health." 42 U.S.C. § 300aa-33(4). Under the *Loving* test, petitioner demonstrates this by showing (1) her condition before the vaccination, (2) her current condition, and (3) that her current condition constitutes a significant aggravation of her prior condition.

In this case, there is no dispute that petitioner had at least some initial symptoms of narcolepsy prior to vaccination and that she developed additional symptoms after the vaccination. (ECF No. 73 (citing Ex. 3, pp. 43, 48); ECF No. 75 (citing Ex. 3, p. 43.)) What is contested, however, is Dr. Steinman's assertion that the Gardasil vaccine "changed the trajectory" of her condition. (Ex. 14, pp. 6, 31; ECF No. 75, p. 40.) There are two cases, *Locane* and *Sharpe,* that illustrate the Circuit's significant aggravation analysis with regard to the evolution of petitioner's clinical course. *Locane v. Sec'y of Health & Human Servs.*, 685 F.3d 1375 (Fed. Cir. 2012); *Sharpe v. Sec'y of Health & Human Servs.*, 964 F.3d 1072 (Fed. Cir. 2020).

In *Locane*, petitioner alleged her Crohn's disease, an inflammatory bowel disease, was significantly aggravated by the hep B vaccine. *Locane*, 685 F.3d at 1377-78. The special master determined that petitioner failed to show "by a preponderance

of the evidence that she was entitled to compensation under the significant aggravation theory because the course of her disease was not affected by the vaccination." *Id.* at 1378. The Federal Circuit found that the special master's finding—that petitioner's clinical course was not inconsistent with the disease generally and not affected by the vaccinations—was considered from "the relevant evidence of record, [drawn from] plausible inferences and articulated a rational basis for the decision," therefore, the decision was not arbitrary or capricious. *Id.* at 1381-82. The Court continued, stating that petitioner was "given ample opportunity to develop her significant aggravation claim but 'failed to present persuasive evidence that separates [her] problems from an expected course of Crohn's disease.'" *Id.* at 1382.

In *Sharpe,* petitioner alleged L.M. had a pre-existing "seizure disorder" and the administration of the several childhood vaccines at her six-month wellness check-up significantly aggravated L.M.'s pre-existing condition. *Sharpe*, 964 F.3d at 1076-77. The special master denied petitioner's significant aggravation claim because L.M.'s genetic mutation, and not the vaccination, was the sole, substantial cause of L.M.'s seizure disorder. *Id.* at 1080. The Circuit found the special master's analysis "required [p]etitioner to prove the expected outcome for a child with a DYNC1H1 gene mutation and to show that L.M.'s current, post-vaccination condition was worse than that expected outcome." *Id.* at 1081. The Circuit stated, "a court should consider all evidence in the record, including evidence of other possible sources of injury. There is, however, a fine line between a court properly considering evidence in the record . . . and improperly placing the burden on the petitioner to prove that her significantly aggravated condition was not caused by her gene mutation." *Id.* at 1082. The Court distinguished the special master's decision from *Locane* stating, in *Locane* "the special master did not require the petitioner to prove that her significantly aggravated condition was not caused by her preexisting condition. Instead, the special master found that the petitioner's condition 'was not affected by the vaccination.'" *Id.*

In this case, petitioner presented to the emergency department on May 11, 2013, with symptoms of sleep disruption and daytime sleepiness with prolonged napping 4-6 weeks prior to her hospitalization. (Ex. 3, p. 42; Ex. 4, p. 52.) Several other physicians also noted sleep disruption and daytime sleepiness with prolonged napping prior to her hospitalization. (Ex. 3, p.43, Ex. 4, p. 52 (Dr. Neiderman); Ex. 3, p.85 (Dr. Martinez); Ex. 3, pp. 5-6, Ex. 4, p. 9, Ex. 11, p. 31 (Dr. Dubrovsky); Ex. 3, p. 66 (Dr. Brown); Ex. 3, p. 48 (Dr. Maragh), Ex. 3, p. 54 (Dr. Chiang); Ex. 3, 69 (Dr. Gutierrez).) In one note, petitioner described "waking up 1-2 [times] a night 4 weeks ago." (Ex. 3, p. 5.) This would place onset of petitioner's symptoms in approximately April 2013, prior to the vaccination at issue. Petitioner reported additional symptoms between 2-4 weeks prior to hospitalization, including: legs buckling (Ex. 3, p. 65, Ex. 3, p. 85), falls (Ex. 3, p. 65, Ex. 3, p. 69), slurred speech (Ex. 3, pp. 5-6), and gait difficulties (Ex. 3, p. 68, Ex. 3, p. 85).

Dr. Deak explains that the full narcoleptic tetrad of symptoms–excessive daytime sleepiness, cataplexy, hypnagogic/hypnopompic hallucinations and sleep paralysis–is rarely present at initial presentation. (Ex. A, p. 5.) The order in which symptoms appear

can also vary. (*Id.* (citing Dauvilliers et al., s*upra,* at Ex. H).) Due to the "insidious onset" of narcolepsy, as well as accompanying behavioral, metabolic, and mood symptoms, narcolepsy is often misdiagnosed. (Ex. A, p. 5.) In fact, petitioner's case "followed a typical time course for pediatric narcolepsy," with excessive daytime sleepiness and nocturnal sleep disruption as her initial symptoms. (*Id.* at 6.) Dr. Deak explains that "[i]t is not surprising that [petitioner] developed cataplectic active phenomenon, in addition to negative phenomenon already present, as her symptoms progressed." (Ex. GG, p. 1.) I am persuaded by Dr. Deak's assessment of petitioner's progression of narcolepsy: petitioner exhibited "symptoms represent[ing] a clear change from [petitioner's] baseline" and a "significant alteration in functioning" well before her vaccination. (Ex. A, p. 4)

Dr. Steinman suggests that, although petitioner reported symptoms prior to the May 1, 2013 immunization, "there was clear worsening" approximately 10 days after the May 1, 2013, Gardasil shot. (Ex. 14, p. 31.) He quotes the "history of present illness" in Dr. Lazar's discharge summaries from May 16, 2013 which details "twitching" episodes in petitioner's left upper extremity and left leg, as well as episodes of light headedness and falling.[29] (*Id.* (*See* Ex. 11, p. 2.) Dr. Steinman stresses that "[t]his type of activity was NOT present prior to the May 1, 2013, immunization, based on the contemporaneous record." (*Id.*) (emphasis in original). Petitioner also asserts that her case of narcolepsy is an "outlier," one which presented with a "fast evolution and diagnosis." (ECF No. 73, p. 30.) Though petitioner notes that she suffered many of the hallmark symptoms of narcolepsy, she contends that she "did so in a seemingly abbreviated time frame compared to many children." (*Id.*) Citing to the Aran et al. study, petitioner suggests that petitioner's case falls within a time frame of three months between onset of sleepiness in children and development of cataplexy. (*Id.* at 29.)

Yet the authors of that study report that "[c]ataplexy occurred *within* 3 months of onset in 85% of cases," and within 2 months of onset in 82% of cases. (Aran et al., *supra,* at Ex. I.) These time frames fit squarely with the progression of petitioner's alleged symptoms. Additionally, the medical records suggest that petitioner was already experiencing symptoms suggestive of cataplexy prior to her vaccination. In fact, several providers documented symptoms of cataplexy, including legs buckling (Ex 3. pp. 65, 85, 90), falls (Ex. 3, pp. 65, 85), slurred speech (Ex. 3, pp. 5-6, 51),[30] and gait difficulties (Ex. 3, p. 68) during the 2-4 weeks prior to hospitalization. The providers

[29] (*See* Ex. 3, p. 43 (On May 11, 2013 "[m]other reports slurred speech and hands twitching and shaking started 3 days ago, knees twitching (while standing) started 2.5 weeks ago and the sleeplessness started 6 weeks ago.); (Ex. 3, p. 48 (On May 11, 2013 "[o]ver the past three days [petitioner] report[ed] "twitching" of her left upper extremity and left leg"); (Ex. 3, p. 71 (same)).

[30] Dr. Neidenberg's narrative from May 11, 2013 states that "slurred speech and hands twitching and shaking started 3 days ago." (Ex. 3, p. 43.) While Dr. Deray's report from June 27, 2013 suggests that petitioner's slurred speech began approximately four days after the Gardasil shot. (Ex. 9, p. 6.) Petitioner's discharge summary, which petitioner's mother claims is the most accurate summary of petitioner's onset of symptoms, simply notes that "Mother reports that at time patient's speech was noted to be 'slurred,'" without any indication of onset. (Ex. 11, p. 2.)

documented the presence of the above symptoms preceding vaccination based on real-time interviews with petitioner and her mother.

In light of the above, I do not find preponderant evidence on this record that petitioner's vaccination significantly aggravated her condition. I have not required petitioner to prove that her post-vaccination condition was worse than the expected outcome. Instead, I find that the evidence taken as a whole shows that her course was not inconsistent with pediatric narcolepsy generally and that her condition was not affected by the vaccination. This finding is consistent with *Locane*. It is also further reinforced by the discussion of the treating physician opinions below.

c. Logical sequence of cause and effect showing the vaccination was the reason for the injury (*Althen* prong two/*Loving* prong five)

The second *Althen* prong/fifth *Loving* prong requires proof of a logical sequence of cause and effect showing that the vaccine was the reason for the injury, usually supported by facts derived from a petitioner's medical records. *Althen*, 418 F.3d at 1278; *Andreu*, 569 F.3d at 1375–77; *Capizzano v. Sec'y of Health & Human Servs.*, 440 F.3d 1317, 1326 (Fed. Cir. 2006); *Grant*, 956 F.2d at 1148. However, medical records and/or statements of a treating physician do not *per se* bind the special master to adopt the conclusions of such an individual, even if they must be considered and carefully evaluated. *See* 42 U.S.C. §300aa-13(b)(1) (providing that "[a]ny such diagnosis, conclusion, judgment, test result, report, or summary shall not be binding on the special master or court"); *Snyder v. Sec'y of Health & Human Servs.*, 88 Fed. Cl. 706, 746 n.67 (2009) ("there is nothing ... that mandates that the testimony of a treating physician is sacrosanct—that it must be accepted in its entirety and cannot be rebutted"). Dr. Steinman's assessment of a vaccine-caused "change in trajectory" is addressed above. Here, I additionally note that there is not preponderant evidence that petitioner's treating physicians concluded that her HPV vaccination caused a significant aggravation of her preexisting narcolepsy.

The medical record closest to supporting petitioner's contention is Dr. Dubrovsky's note that petitioner "presented with excessive daytime sleepiness, cataplexy, and episodes of sleep paralysis since mid April, exacerbated after Gardasil shot at the end of April." (Ex. 11, p. 31.) At this visit, Dr. Dubrovsky also recommended reporting petitioner's condition "to the registry" (presumably referring to the Vaccine Adverse Event Reporting System (VAERS). (*Id*.) Importantly, however, she made a point of specifically noting in the same assessment that "I am not certain[] if the symptoms are associated with the vaccination." (*Id*.) Dr. Dubrovsky previously wrote that she "*wonder[ed]* if the vaccination ha[d] anything to do with the escalating of the symptoms." (Ex. 3, p. 6.) Considering Dr. Dubrovsky's records as a whole, her statements of mere suspicion fall short of an opinion supporting a vaccine-related significant aggravation of petitioner's condition. *See Stapleford v. Sec'y of Health & Human Servs.,* No. 03-234V, 2009 WL 1456441, at *17 n.24 (Fed. Cl. Spec. Mstr. May 1, 2009) (referencing medical record "is quite different from an indication that such physician has reached a *conclusion* concerning a causal relationship") (emphasis in

original), *aff'd*, 89 Fed. Cl. 456 (Fed. Cl. 2009). Moreover, "[a] treating physician's recognition of a temporal relationship does not advance the analysis of causation." *Isaac v. Sec'y of Health & Human Servs*., No. 08-601V, 2012 WL 3609993, at *26 (Fed. Cl. Spec. Mstr. July 30, 2012); *see also Devonshire v. Sec'y of Health & Human Servs.,* No. 99-031V, 2006 WL 2970418, at *19 (Fed. Cl. Spec. Mstr. Sept. 28, 2006) (medical expert's "*post hoc ergo prompter hoc* reasoning…has been consistently rejected by the Court and is 'regarded as neither good logic nor good law'") (quoting *Fricano v. U.S.,* 22 Cl. Ct. 796, 800 (1991) (emphasis in original)).

The records from petitioner's other treating physicians regarding causation were no less equivocal. Pediatric neurologist Dr. Martinez questioned whether petitioner's symptoms "could possibly be a side effect of Gardasil," but ultimately concluded that the "etiology of [petitioner's] symptoms [is] unknown" and speculated that her symptoms could be due to green coffee extract that petitioner was taking. (Ex. 3, pp, 90, 102.) Dr. Stuart Brown also questioned whether petitioner's Gardasil vaccination "triggered [] narcolepsy on an autoimmune basis," noting that "[t]his has been reported occasionally with other immunizations," but with respect to Gardasil, "the statistics for this are questionable as to a cause and effect relationship." (*Id.* at 66.) Pediatric infectious disease specialist Dr. Robert Reid also examined petitioner and concluded that her condition was "not likely a reaction to the vaccine since the symptoms of insomnia started way before the vaccine was given." (*Id.* at 53.) Dr. Gutierrez, a second pediatric infectious disease specialist, observed that petitioner "had received the Gardasil [vaccine] after the symptoms had started" and did "not believe there has been any association." (*Id.* at 70.)

On the whole, I find that petitioner's treating physicians considered, though did not conclude, that petitioner's HPV vaccine significantly aggravated her preexisting narcolepsy. *See Cedillo v. Sec'y of Health & Human Servs.*, 617 F.3d 1328, 1348 (Fed. Cir. 2010) (special master did not err in affording little weight to the opinions of petitioner's treating physicians where "none of the treating physicians concluded that the MMR vaccine caused [petitioner's] autism"); *Moberly*, 592 F.3d at 1324-25 (finding no treating physician evidence to support the claim of causation where the "medical records regarding the temporal proximity of the [vaccination] to the seizures were all speculative.")

Other records suggest that petitioner's treating physicians considered Gardasil as a possible cause of petitioner's narcolepsy in large part due to her mother's prompting. (*See* Ex. 3, p. 100 ("[m]other has concerns that the [petitioner] had a Gardasil [*sic*] immunization at [*sic*] this may have contributed to the [petitioner's] symptoms"); Ex. 48, p. 29 (petitioner's "mom related [daughter's illness] to the gardasyl [*sic*] shot"); Ex. 3, pp. 62-63 (petitioner's "mother believes that some of [petitioner's] symptoms have occurred shortly after her Gardasil vaccination.")) That petitioner's treating physicians noted her mother's concerns in their records, however, provides little support for the proposition that they themselves believed Gardasil to be a cause for petitioner's condition. *E.g., Moriarty by Moriarty v. Sec'y of Health & Human Servs.,* No. 03-2876V, 2014 WL 4387582, at *15 (Fed. Cl. Spec. Mstr. Aug. 15, 2014) (petitioner's

parent's "views about causation are not persuasive because she is not a medical doctor'"), *review denied, decision aff'd,* 120 Fed. Cl. 102 (2015), *vacated and remanded on other grounds,* 844 F.3d 1322 (Fed. Cir. 2016); *accord* 42 U.S.C. § 300aa–13 (a special master may not find in favor of the petitioner "based on the claims of a petitioner alone, unsubstantiated by medical records or medical opinion"); *James-Cornelius v. Sec'y of Health & Human Servs.,* 984 F.3d 1374, 1380 (Fed. Cir. 2021) ("lay opinions as to causation or medical diagnosis may be properly characterized as mere 'subjective belief' when the witness is not competent to testify on those subjects[.]")

Lastly, petitioner also contends that "[t]here is no evidence of another factor that may have exacerbated her narcolepsy." (ECF No. 73, p. 27.) In this Program, however, absence of another cause is not persuasive evidence in support of petitioner's burden to show causation. *See D.G.,* 2019 WL 2511769, at *183 ("[T]he Federal Circuit in *Grant* state[]d [that] petitioner's burden is to prove vaccine causation with affirmative evidence. Saying since there is no other cause, it has to the vaccine is not affirmative proof.") (citing *Grant,* 956 F.2d at 1149).

d. Proximate temporal relationship between vaccination and injury (*Althen* prong three/*Loving* prong six)

The third *Althen* prong/sixth *Loving* prong requires establishing a "proximate temporal relationship" between the vaccination and the injury alleged. *Althen*, 418 F.3d at 1281. That term has been equated to the phrase "medically-acceptable temporal relationship." *Id.* A petitioner must offer "preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation." *de Bazan v. Sec'y of Health & Human Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008). The explanation for what is a medically acceptable timeframe must also coincide with the theory of how the relevant vaccine can cause an injury. *Id.*; *Shapiro v. Sec'y of Health & Human Servs.*, 101 Fed. Cl. 532, 542 (2011), *recons. den'd after remand*, 105 Fed. Cl. 353 (2012), *aff'd mem.*, 503 Fed. Appx. 952 (Fed. Cir. 2013); *Koehn v. Sec'y of Health & Human Servs.*, No. 11–355V, 2013 WL 3214877, at *26 (Fed. Cl. Spec. Mstr. May 30, 2013), *mot. for review den'd* (Fed. Cl. Dec. 3, 2013), *aff'd*, 773 F.3d 1239 (Fed. Cir. 2014).

Petitioner received her second HPV vaccination on May 1, 2013. (Ex. 4, pp. 70-71.) Petitioner was subsequently hospitalized ten days later, on May 11, 2013. (Ex. 3, p. 43.) Thus, petitioner contends that her medical records show "an increase of narcolepsy symptoms in the span of four to ten days after receipt of the May 1, 2013 vaccination." (ECF No. 73, p. 31.) However, petitioner's *Althen* prong three / *Loving* prong six argument lacks a reliable medical or scientific explanation for how her HPV vaccine significantly aggravated her narcolepsy. Dr. Steinman relies solely on literature evaluating the onset of narcolepsy following the administration of another vaccine, the Pandemrix H1N1 influenza vaccine, to establish a temporal relationship between the HPV vaccination and worsening of petitioner's narcolepsy. (Ex. 14, pp. 32-33 (discussing Partinen et al., *supra,* at Ex. 38; Winstone et al., *supra,* at Ex. 39).)

Although the timing in this case is consistent with what is generally thought to be an appropriate timeframe for the adaptive immune response underlying the molecular mimicry theory in other contexts, the specific data from these Pandemrix studies cannot be extrapolated to the HPV vaccine where an increased risk of narcolepsy has not been shown. (*See* Arnheim-Dahlstrom et al., *supra,* at ECF No. 26; Hvid et. al., *supra,* at Ex. FF.) This is especially true "in a case like the present, where a vaccine's formulation bears heavily on [p]etitioner's claim[.]" *D'Tiole,* 2016 WL 7664475, at *22 (citations omitted). Where "[p]etitioner wants to leverage findings about a different vaccine formulation [and] epidemiologic evidence relevant to the version of the vaccine in dispute," here the HPV vaccine, such findings "ought to be weighed against [p]eitioner's proof in evaluating whether [s]he has carried h[er] overall burden." *Id.*

VII. Conclusion

Petitioner has my sympathy for the pain and suffering she endured during her hospitalization and the symptoms she suffers from presently. However, for all the reasons discussed above, after weighing the evidence of record within the context of his program, I cannot find by preponderant evidence that the HPV vaccine significantly aggravated petitioner's narcolepsy. Accordingly, this claim is **DISMISSED.**[31]

IT IS SO ORDERED.

s/Daniel T. Horner
Daniel T. Horner
Special Master

[31] In the absence of a timely-filed motion for review of this Decision, the Clerk of the Court shall enter judgment accordingly.